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VILNIUS UNIVERSITY

Vykinta PARČIAUSKAITĖ

# Gamma range auditory-steady state responses as correlates of individual cognitive performance

DOCTORAL DISSERTATION

Natural Sciences, Biophysics N 011

VILNIUS 2022

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VILNIAUS UNIVERSITETAS

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# Gama diapazono klausos nuostovieji atsakai, kaip individualių kognityvinių gebėjimų koreliatai

DAKTARO DISERTACIJA

Gamtos mokslai, Biofizika, N 011

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# ABBREVIATIONS

| ABR     | Auditory brainstem response  |
|---------|--|
| AEP     | Auditory evoked potential  |
| ADAS    | Alzheimer's Disease Assessment Scale                                     |
| AM      | Amplitude modulated  |
| ASD     | Autism spectrum disorders  |
| ASSR    | Auditory steady-state response   |
| BACS    | Brief Assessment of Cognition in Schizophrenia                           |
| BRB-N   | Brief Repeatable Battery of Neuropsychological Tests                     |
| CVLT    | California Verbal Learning Test  |
| DLPFC   | Dorsolateral prefrontal cortex   |
| EEG     | Electroencephalography   |
| EFR     | Envelope-following response  |
| ERP     | Event-related potential  |
| ERSP    | Event-related spectral perturbation                                      |
| GABA    | Gamma-aminobutyric acid  |
| GBR     | Gamma-band responses   |
| IGF     | Individual gamma frequency   |
| LLR     | Late-latency responses   |
| MEG     | Magnetoencephalography   |
| MLR     | Middle-latency responses   |
| MATRICS | Measurement and Treatment Research to Improve Cognition in Schizophrenia |
| MCCB    | MATRICS Consensus Cognitive Battery                                      |
| PLI     | Phase-locking index  |
| RT      | Response time  |
| SD      | Standard deviation   |
| STFT    | Short-time Time Fourier Transform  |
| tACS    | Transcranial alternating current stimulation                             |
| WAIS    | Wechsler Adult Intelligence Scale  |
| WRAT    | Wide Range Achievement Test  |
|         |  |

#### 1. INTRODUCTION

Electroencephalographic (EEG) gamma frequency (30-80 Hz) is related to information processing that occurs during various sensory and cognitive processes (Crone et al., 2001; Kaiser et al., 2017; Steinmann et al., 2014; Villena-González et al., 2018). Moreover, when cognitive and/or perceptual processes are impaired, such as in neuropsychiatric disorders, EEG responses in the gamma range are often also affected (Herrmann and Demiralp, 2005; Tallon-Baudry and Bertrand, 1999). One approach to study the individual characteristics of neural synchronisation in the gamma range is to elicit a brain electrophysiological response by periodic auditory stimulation, known as an auditory steady-state response (ASSR). The ASSR to auditory stimulation is highest when stimuli are presented at around 40 Hz (Picton, 2013; Picton et al., 2003a). Disturbances of 40 Hz ASSRs parameters (e.g. event-related spectral perturbation (ERSP) and phase-locking index (PLI)) are observed in the presence of neuropsychiatric disorders and at high risk of such disorders (Hamm et al., 2011; Rass et al., 2012; Tada et al., 2016). In these conditions, the 40 Hz ASSR is often taken as an indicator of altered cognitive processing (Kirihara et al., 2012; Leonhardt et al., 2020; Light et al., 2006; Puvvada et al., 2018; Rass et al., 2012; Sun et al., 2018).

This assumption that ASSR and cognitive functions are linked is supported by several facts. First, despite the major contribution from the auditory cortex, the thalamo-cortical networks also are involved in ASSR generation (Bish et al., 2004; Pastor et al., 2002; Reyes et al., 2004), with the latter being important for information transmission and processing (Chen et al., 2019). Second, 40 Hz ASSRs are regulated by arousal and attention states (Gander et al., 2010; Górska and Binder, 2019; Griškova et al., 2007; Griškova-Bulanova et al., 2011; Skosnik et al., 2007; Voicikas et al., 2016) that are closely connected to cognitive abilities (Logue and Gould, 2004). Third, it was shown that the gamma-range ASSRs are associated with the degree of cognitive deterioration in individuals with Alzheimer's disease and mild cognitive impairment (van Deursen et al., 2011). Additionally, ASSRs are associated with working memory, attention, reasoning, problem-solving skills, metacognition, and insight in schizophrenia patients (Kirihara et al., 2012; Leonhardt et al., 2020; Light et al., 2006; Puvvada et al., 2018; Rass et al., 2012; Sun et al., 2018). The abovementioned indicate that gamma-range ASSRs, particularly around 40 Hz, may represent the neurobiological mechanisms underpinning cognitive functions.

However, the direct analysis of the relationship between parameters of 40 Hz ASSRs and the cognitive functions is limited to several studies. Of

those, few studies failed to establish a link between ASSR and cognitive characteristics in patients and controls, or the correlations discovered in patients were not observed in the healthy control group, such as the association between ASSRs and working memory (Kirihara et al., 2012; Light et al., 2006; Tada et al., 2016). These findings imply that gamma-range ASSRs do not always encounter the activation of brain networks involved with cognitive processes. However, the investigated samples were diverse in terms of participant age and gender composition, both of which have previously been shown to modulate ASSRs (Griškova-Bulanova et al., 2013; Melynyte et al., 2018). In addition, none of the studies carried out a comprehensive assessment of cognitive abilities, covering both simple (involving only sensory perception) and complex (requiring higher-level cognitive processes) information processing. Therefore, in order to determine whether ASSR can be used as a biomarker of cognitive impairment, it is first necessary to investigate the relationship between cognitive abilities and 40 Hz ASSR in homogeneous groups of subjects by measuring different cognitive abilities and by determining the association of each of these abilities with ASSR (Kirihara et al., 2012; Oda et al., 2012).

Another reason why the relationship between cognitive function and ASSR is not yet fully understood may be that the most common frequency of ASSR in studies is 40 Hz. Although cognitive impairments are often connected with 40 Hz ASSR disturbances (Light et al., 2006), these are not limited to this frequency (Lehongre et al., 2011; Rass et al., 2012). Nevertheless, most studies focus on this or other specific ASSR frequency, while the individual resonance frequency in the gamma band, also known as individual gamma frequency (IGF) (Baltus et al., 2018; Baltus and Herrmann, 2016, 2015), has largely gone unexplored. IGF indicates the frequency at which the brain reacts the strongest when stimulated compared to other frequencies. The IGFs can be detected when multiple stimulation frequencies under the range of interest are tested (Zaehle et al., 2010). The IGFs can also be found by examining the envelope-following response (EFR). EFR is a steady-state response that follows the envelope of a stimulating waveform (Dolphin, 1997). In the case of the chirp stimulation, EFR covers a wide range of frequencies in one sweep (Purcell et al., 2004). Because the preferred oscillation frequencies of networks are determined by their anatomical properties and the speed of neuronal communication (Buzsáki and Draguhn, 2004), IGF may more accurately reflect the characteristics of individual networks than the commonly used 40 Hz ASSRs. Thus, the key to understanding the connection between ASSR and cognitive function may not be a single frequency, such as 40 Hz, but rather a person-dominant frequency within the gamma range (Zaehle et al., 2010).

Hence, although changes in gamma-band ASSRs are associated with cognitive impairment, their links are not yet fully understood. In order to further explore these links, it is first necessary to assess the evidence in the scientific literature, to systematise it and to identify areas for future research, i.e., to perform a systematic review. Second, given the incompleteness and comparative nature of the studies to date, there is a need for studies to further investigate the relationship between 40 Hz ASSR and cognitive abilities (covering both simple and complex information processing) in a homogeneous (i.e., age- and sex-matched) sample of healthy subjects. Thirdly, the ASSR frequency with the highest amplitude response, also known as the IGF, may more accurately reflect the characteristics of an individual's neural networks than the commonly used 40 Hz ASSR; hence it is also important to assess the relation between cognitive abilities and the ASSR at the IGF of each subject.

#### 1.1 Aim and objectives

This work aimed to investigate the relationship between cognitive performance and measures of ASSR in the gamma frequency range. The objectives were as follows:

- 1. To conduct a critical systematic review of the literature on the relationship between cognitive performance and gamma-range ASSR parameters.
- 2. To explore the relationship between cognitive performance and parameters of 40 Hz ASSR in a sample of young healthy subjects.
- 3. To explore the relationship between cognitive performance outcomes and the measures of EFR at 40 Hz and IGF in a sample of young healthy subjects.

## 1.2 Scientific novelty

- 1. For the first time, a critical systematic review of the literature on the link between cognitive performance and 40 Hz ASSR parameters was conducted.
- 2. For the first time, the relationship between 40 Hz ASSR and cognitive abilities related to processing simple and complex information was investigated in detail in a sample of young, healthy men.
- 3. For the first time, in a sample of young, healthy subjects, the association between ERP, at 40 Hz and IGF, and cognitive abilities related to processing of simple and complex information was analysed.

### 1.3 Practical implications

- 1. Gamma-range ASSRs can be used to index neural mechanisms of information transfer underlying cognitive processing.
- 2. Gamma-range ASSRs can be used as an individual biological marker for disturbed cognitive functioning in neuropsychiatric diseases.
- 3. IGF can be used to explore the unique characteristics of the individual network more accurately.

### 1.4 Statements to be defended

- 1. A systematic review of the literature revealed that individual differences in gamma-range ASSR might reflect abilities to control attention and temporarily store and process information.
- 2. The event-related spectral perturbation and phase-locking index of 40 Hz ASSR positively correlate with the mean number of steps on the Tower of London task in a sample of young, healthy males.
- 3. The event-related spectral perturbation and phase-locking index of the EFR at the 40 Hz and IGF negatively correlate with the performance speed on the Tower of London task.

#### 2. LITERATURE REVIEW

#### 2.1 Electroencephalography

In 1924, Hans Berger developed the technique to offer a "window onto the brain", which now is termed electroencephalography (EEG) (Berger, 1924). The discovery of human EEG is frequently regarded as a watershed moment in the history of neuroscience: it established the first technology capable of analysing the electrical activity of a living brain with a temporal resolution of between a few milliseconds. Since human information processing occurs in the millisecond time range, EEG is a good technique for evaluating the brain's response and processing of information in human participants while doing various tasks under different conditions. This makes EEG a convenient method for studying neurological conditions, brain development and psychopathology (Knyazev et al., 2003; Mari-Acevedo et al., 2019). Typically, the EEG is described in terms of amplitude (10 to 100 microvolts), frequency and phase. These parameters exhibit a high degree of stability, reliability, and specificity and are thus regarded as biomarkers (Turetsky et al., 2007).

There are two distinct types of neuronal activation: (1) rapid depolarisation of the neuronal membranes, which results in the 1-2 ms action potential and is mediated by the sodium and potassium voltage-dependent ionic conductance, (2) slower changes in membrane potential caused by synaptic activation, arising from multiple neurotransmitter systems (Kirschstein and Köhling, 2009). While action potentials demonstrate the most prominent changes in neuronal potential, they are highly asynchronous and many action potentials have to accumulate at the same time in order to record EEG signals. However, synaptic activity is sufficiently long-lasting to be a major generator of EEG potentials (Da Silva, 2009; Olejniczak, 2006). Thus, the EEG is the result of the summation of synaptic activity and therefore bears little resemblance to the excitatory processes of individual neurons. Furthermore, EEG results are affected by uncertainties in the conductivity of the soft and hard tissues between the current source and the recording electrode (Buzsáki et al., 2012). Therefore, the spatial resolution of EEG at the macroscopic level is limited.

Postsynaptic potentials could be excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs). The excitatory or inhibitory activity reflects the type and number of neurotransmitters generated at the synapse at any given time, the type of receptors, and their interaction with specific ion channels and intracellular subcarriers (Da Silva, 2009;

Raghavan et al., 2019). When EPSPs and IPSPs emerge synchronously in clusters of radially aligned apical dendrites, they can be detected on the scalp's surface; if the neurons produce an EPSP, the negative voltage difference is detected on EEG, and in reverse, if the neurons produce IPSP, the positive voltage difference is seen. Thus, the EEG captures brain activity by summing up all the excitatory and inhibitory postsynaptic potentials generated by large groups of synchronously activated cortical pyramidal neurons — a microvolt potential generated by about 60 million vertical dipolar units perpendicular to the scalp (Lopez-Gordo et al. 2014).

EEG is mainly driven by vertically oriented pyramidal neurons located in cortical layers III, V, and VI, organised into cortical columns (Olejniczak, 2006). Approximately 80 % of all cortical neurons in mammals are excitatory pyramidal cells (DeFelipe, 2011), and cortical pyramidal neurons are also excellent dipoles due to their specific anatomical configuration with a long apical dendrite perpendicular to the cortical surface (Kirschstein and Köhling, 2009). Dendrites oriented perpendicularly to the cortical surface generate not only an electric field but also a magnetic field on the outside of the head, and are thus involved in the generation of both EEG and magnetoencephalography (MEG) signals.

The EEG signal reveals rhythmic patterns of neuronal activity that are consistent with patterns of behaviour. Delta (0.5-3.5 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz) and gamma (>30 Hz) are common names for EEG frequency ranges. The predominantly lower frequencies correspond to highly synchronized activity, such as dreamless sleep and unconscious states (Singh et al., 2016) and are generated by the widespread excitatory neurons that project throughout the thalamus and cortex (Neske, 2016). In contrast, higher frequencies correspond to relatively unsynchronised activity and are generated by more localised interactions between interneurons and pyramidal cells in the cortical and thalamo-cortical projections, which are involved in specific information processing (Macdonald et al., 1998; Ribary et al., 2017).

Gamma-band activity (30-80 Hz), which lies between the higher frequencies of the EEG, has received much attention as it is involved in various information processing operations such as sensory discrimination, attentional learning and memory (Kaiser and Lutzenberger, 2003). This activity acts as a selective mechanism for the transmission of sensory information in distributed neural circuits (Adaikkan and Tsai, 2020): artificial generation of gamma oscillations using optically activated ion channels has been shown to improve the perception of stimuli (Knoblich et al., 2010). Gamma oscillations may be classified as spontaneous, induced, and evoked gamma activity (Galambos, 1992). Spontaneous gamma oscillations are a substantial component of the brain's constant background activity and occur spontaneously during rapid eye movement sleep (REM), slow-wave sleep, under various anaesthetics and in a relaxed state (Dang-Vu et al., 2008). Gamma-range activity which is not phase-locked to stimulus onset is called induced gamma activity. The induced oscillations are task-dependent, occur 200-400 ms after stimulus onset and are linked with associative learning, sensorimotor integration, feature binding (Brosch et al., 2002). The most commonly studied are gamma-band oscillations caused by periodic external stimuli (exogenous rhythms). These stimuli often synchronise with endogenous sensory input rhythms, a phenomenon known as neural entrainment (Schroeder and Lakatos, 2009).

#### 2.1.1 EEG signal acquisition

An internationally recognised standard of EEG electrodes placement is the 10/20 system (Fig. 2.1), adopted in 1958 (Jasper, 1958). This standard establishes uniform physical arrangement and labelling of electrodes on the scalp. The scalp is divided into 10-20 % proportional to the prominent features of the skull: nasion, preauricular points and inion. The following abbreviations are used to denote the locations of the electrodes: F (frontal), C (central), T (temporal), P (posterior), and O (occipital). On the left side of the skull there are odd numbers next to the letters and on the right side there are even numbers (Fig. 2.1). However, the limited spatial resolution of the 10/20 system makes it difficult to locate the areas of the scalp where activity occurs (Michel and Brunet, 2019). Therefore, the 10/20 system is occasionally extended to higher electrode density configurations, such as 10/10 and 10/5, which can contain almost 300 electrode sites (Jurcak et al., 2007).



**Figure 2.1** Electrode locations of International 10-20 system for EEG recording.

Silver and silver chloride (Ag/AgCl) electrodes are commonly used for EEG recording. Ag/AgCl electrodes are suitable for low electrode-to-skin impedance, resistant to noise and motion artefacts. The impedance between the recording electrodes and the subject's scalp is one of the important sources of noise in EEG signals. Acceptable impedances are up to  $10 \text{ k}\Omega$ , although less than 5 k $\Omega$  is recommended (Sinha et al., 2016). To obtain appropriate impedance values, it is necessary to maintain a sufficient level of electrode cleanliness and to impregnate the electrodes with a saline electrolyte gel (Fernández and Pallás-Areny, 2000). Unfortunately, the impedance still increases as the gel evaporates, so acceptable EEG data can only be obtained for 90-120 minutes (Kleffner-Canucci et al., 2012). Impedance values greater than 100 k $\Omega$  are considered inappropriate as they often indicate a shunt or short circuit associated with salt bridging in the scalp (Macy, 2015).

EEG measures the potential difference between two electrodes, meaning that the signal displayed on any given channel is the potential difference (10-100 microvolts) (Teplan, 2002). As the ground electrode is connected to the amplifier's ground circuit and is exposed to electrical noise, which affects the voltage difference between the ground and EEG scalp electrodes, the reference channel is selected from the EEG recording channels (Beniczky and Schomer, 2020). For the reference channel, it is very important to select a point sufficiently far away from the power supplies to be considered as a zero-potential reference point, but not too far away to avoid external noise arising in long wires (Liu et al., 2015). Many EEG caps have a predefined reference channel, for example in the FCz or Cz position. The Cz reference point is an

advantageous location because it is centred between the active electrodes (Ríos-Herrera et al., 2019). In other cases, special electrodes can be attached to the nose, the earlobes or the mastoids (the bones behind the ears) (Hagemann et al., 2001). Recording can also be done without a reference point — when using an average reference montage, the average signal is used as the reference signal for each channel (Lemos and Fisch, 1991). The choice of reference point can depend on the quality of the recording; for example, topographic distortion can occur if a relatively electrically neutral area is not used (Trujillo et al., 2017). On the other hand, the average reference montage includes the activity of the electrode of interest and the potential amplitude will vary depending on the number of electrodes (Acharya and Acharya, 2019).

#### 2.1.2 EEG signal processing

During recording, the EEG captures not only the physiological activity of the cortex, but also the electrical fields generated by a variety of other sources, such as cardiac, myogenic and electromagnetic ones, known as artefacts (Urigüen and Garcia-Zapirain, 2015). Signals with a relatively limited and predictable frequency range, such as power lines at 50 Hz, can be removed using a notch filter (Repovs, 2010; Tandle and Jog, 2015). More sophisticated filtering techniques, such as adaptive filtering or threshold filtering with wavelet transform, are also used to remove EEG artefacts. The basic mechanism of adaptive filtering is to iteratively adjust the weights according to an optimisation algorithm to determine the amount of artefactual contamination in the original input and to subtract it from the EEG signal containing artefacts (Jiang et al., 2019). Thresholding using a wavelet transform can also be applied to remove signals containing artefacts; a cleaner signal is then recovered by summing the remaining components (Jiang et al., 2019).

EMG-related artefacts such as eye blinking, gnashing of teeth, shoulder or leg movements can be avoided by instructing subjects to avoid excessive blinking, swallowing, moving or gnashing of teeth (Usakli, 2010). However, some movements are unavoidable. Independent component analysis (ICA) proven to be an effective method to separate artefact processes, as the signal of brain activity and the artefacts unrelated to that activity are independent of each other in both time and space (Delorme et al., 2007; Chen et al., 2015). Components are extracted from the original signals, then the clean signal is reconstructed. Oculomotor artefacts are also removed using regression analysis, by subtracting the horizontal and vertical electrooculogram (EOG) channel signals from the contaminated EEG (Croft et al., 2005). If the reference electrode responds to artefactual electrical activity, affecting the EEG traces of all electrodes, then successful analysis of the contaminated recordings often requires re-referencing procedures to minimise this effect (Kayser and Tenke, 2010). However, if the artefacts mimic the structure of the EEG, their inclusion in a fully automated rejection procedure can severely affect the results and ultimately lead to misinterpretations, which is why manual rejection is also commonly used.

#### 2.2.3 Event-Related Potentials

In a continuous real-time EEG, the amplitude of individual responses to stimuli is small and cannot be assessed effectively. Thus, to highlight an EEG activity induced by stimulus exposure, the same stimulus must be repeated numerous times depending on the magnitude of its effect (Owen, 2004). The averaging process reduces random EEG changes unrelated to the stimulus, resulting in potentials associated with the simulation, known as event-related potentials (ERPs) (Beres, 2017).

Each ERP can have both positive and negative components, denoted by their amplitude polarity (P or N) and latency, e.g., N100 (N1), P200 (P2), P300 (Woodman, 2010). The early waves or components, which peak within the first 100 ms of stimulus onset, are mainly dependent on the physical properties of the stimulus; these are called exogenous or sensory responses. The later amplitude peaks reflect the processing of information about the stimulus, and are referred to as endogenous or cognitive responses (Sur and Sinha, 2009). However, the early components of ERPs can also provide crucial information about cognitive processes, as they show automatic attention and early memory processes necessary for higher-level cognitive functioning (Luck et al. 2000). ERPs are widely used in cognitive neuroscience and psychology research because they can shed light on how the brain processes information: they explain the temporal sequence of sensory, cognitive, emotional and motor processes in response to stimuli, which is the basis for the definition of the individual components of ERPs (Luck and Kappenman 2013).

Auditory Evoked Potential (AEP) is electrical activity in the brain that is evoked by and time-locked to auditory stimulus. AEP is a valuable diagnostic tool for the functional evaluation of the auditory system, with the primary clinical use in evaluating auditory attention, discrimination, and memory (Frizzo, 2015). Often, AEPs are triggered by broadband auditory clicks generated by unidirectional orthogonal short pulses (40 to 500 ms) with a frequency spectrum below 10 kHz (Edmonds, 2008). AEP responses can be generated passively, without the participant actively participating in the listening activity.

AEPs are classified into three types based on their latencies: (1) short-latency responses also referred to as auditory brainstem responses (ABR), with a latency of < 10 ms, (2) middle-latency responses (MLRs) with a latency of 10-50 ms, and (3) late-latency responses (LLRs) with a latency of > 50 ms (Alhussaini et al., 2018). ABR and MLR are substantially affected by stimulus properties such as sound intensity, frequency, and stimulus onset asynchrony (SOA) (Burkard et al., 2007). The LLR is cortical in origin, with early LLRs depending on the physical properties of the stimuli, while late LLRs also depend on the subject's attention, information processing and stimulus categorisation (Bruno et al., 2016)

ABR consists of positive and negative waves (Fig. 2.2). The ABR waves I and II indicate the activity of the auditory nerve in the distal and proximal parts respectively (De Pascalis, 2004). Waves III, IV and V correspond to the activity of the superior olivary body, the lateral lemniscus and the inferior colliculus (Celesia, 2013; Jewett and Williston, 1971). ABR is commonly used as a screening method for auditory sensitivity and plays an important role in neurotology (Celesia, 2013).



**Figure 2.2** Idealised AEP evoked by transient stimuli, including components dependent on stimulus context and subject attention (figure by MIT OpenCourseware).

LLR can be triggered by a wide range of sounds, such as clicks, pure tones, noise bursts, music, environmental noise and speech sounds (Lunardelo et al., 2019). The first LLRs are the P1, N1 and P2 waves, which peak at approximately 50, 100 and 180 ms after the onset of sound. They are called exogenous because they reflect the physical properties of external events (Alain et al., 2013). Subsequent fluctuations in LLR, N2 and P3 (P300) are considered endogenous as they are modified by psychological variables such as attention and anticipation (Alain et al., 2013; Sur and Sinha, 2009).

#### 2.2 Auditory Steady-State Response

A periodic auditory stimulus produces continuous neural oscillations synchronised with the periodicity of the stimulus; this neural response is called the auditory steady-state response (ASSR) (Miyazaki et al., 2013). Throughout the stimulus presentation, the ASSR maintains phase-locking with the intrinsic fundamental frequency of the stimulus (Regan, 1989). ASSR may be evoked with the amplitude or frequency modulation of up to 485 Hz in younger and up to 235 Hz in older population (Purcell et al., 2004). Nevertheless, this EEG synchronisation to auditory stimulus is often most pronounced when stimulation is delivered at a frequency of 40 Hz, indicating that 40 Hz is the auditory network's preferred working frequency (Picton et al., 1987). Visual and tactile (somatosensory) stimuli may also elicit the steady-state response, with peak frequencies of roughly 10-15 Hz and 26 Hz

correspondingly (Gulbinaite et al., 2017; Snyder, 1992). However, the ASSR peak response at 40 Hz is more pronounced than the peak frequencies of other modalities (Porcu et al., 2014).

#### 2.2.1 ASSR generation hypotheses

Galambos et al. (1981) were the first to show that the response in auditory cortex is most prominent at around 40 Hz. The later study proposed that the 40 Hz ASSR is a juxtaposition of middle-latency responses (Galambos, 1992). Furthermore, Makeig (1990) discovered that stimuli at frequencies below 1 Hz also generate a sequence of 40 Hz oscillations, the gamma-band response (GBR); he also hypothesised that these oscillations overlap and trigger first the MLR at 10 Hz and then the ASSR at 40 Hz (Makeig, 1990). The results of some subsequent studies have confirmed that the 40 Hz ASSR can be effectively described by a superposition of ABR and MLR waves (Tan et al., 2017). It was found that during the formation of a 40 Hz ASSR, the contribution of the Na-Pa and Nb-Pb components of the MLR may be approximately equal (45 % each), while the contribution of the ABR V wave may be lower (10 %) (Bohórquez and Özdamar, 2008).

However, numerous experimental findings contradicted the hypothesis of an overlapping MLR. Firstly, magnetic resonance imaging (MRI) studies have shown that the MLR and the 40 Hz ASSR sources are located at different locations within the auditory cortex, indicating that the ASSR response has a distinct neurological substrate (Gary, 2008). Secondly, it has been shown that amplitude and phase between real and synthetic ASSR are different (Santarelli et al., 1995). Third, ASSR is permanently disrupted by the omission of one click in a sequence of 40 Hz clicks, and ASSR continues after the stimulus has ceased, which cannot be explained by a superposition of responses to each click (Makeig, 1990; Manting et al., 2021).

The oscillatory entrainment theory proposes that ASSR may be the result of the activation of additional mechanisms involving neurons that respond to the preferred modulation frequency (Thut et al., 2011). The theory suggests that entrainment, where exogenous and endogenous oscillations are synchronised or phase-coupled, optimises the perception of rhythmic stimuli, as the phase of high arousal coincides with periods of task-relevant sensory input (Dugue et al., 2011). In this way, regularly time-varying stimuli create periodic "excitation windows" during which sensory perception is enhanced (Dugue et al., 2011). Maintaining a high-excitability state is more metabolically demanding than changing between high and low excitation levels, which is why rhythmic-mode processing is an incredibly efficient way to allocate neural resources to rhythmic inputs (Henry et al., 2014).

#### 2.2.2 ASSR sources

Human ASSR sources are widely examined using dipole source analysis. The locations of ASSR differ depending on frequencies. With modulation frequencies of roughly 80 Hz, ASSR activity sources are mainly located in the brainstem (Wong and Stapells, 2004), while 40 Hz ASSR sources are primarily located in the cortex (Steinmann and Gutschalk, 2011). 40 Hz ASSR activity is strongest in the primary and secondary auditory cortex (O'Donnell et al., 2013). ASSR sources in primary cortex are tonotopically spaced, with higher amplitude modulated (AM) frequencies activating areas closer to medial parts of the auditory cortex (Herdener et al., 2013; Pantev et al., 1996). In addition, ASSRs are typically larger in the hemisphere opposite to the stimulated ear and in the right hemisphere than in the left hemisphere (Ross et al., 2005). Sources located outside the auditory cortices are considered nonprimary ones (Farahani et al., 2018). The 40 Hz ASSR can extend over a wide range of cortical areas (anterior, central, temporal and parietal regions), as well as subcortical areas such as the corpus callosum (medial cortex) and cerebellum (Pellegrino et al., 2019; Reyes et al., 2005). However, the number and location of non-primary sources are still debatable.

Studies reveal some aspects of the frontocentral cortex in generation of ASSR. First, pathological or state-dependent changes in ASSR are observed in frontocentral regions. (Khaleghi et al., 2019). Second, the strengthening of ASSRs through focus is also most pronounced in frontocentral areas, where it increases power by more than 80 %, while in other regions the effect of focus is around 20-25 % (Manting et al., 2020). In addition, the continued oscillation of the ASSR after the stimulus is terminated is mainly generated also by the frontal region (Manting et al., 2021). Furthermore, Tada et al. (2021) found that the ASSR in the parietal cortex has one peak at 40 Hz and the temporal-frontal cortex has two peaks at 40 and 80 Hz. This may be related to the compatibility of local neuronal circuits being tuned to different frequencies in the respective lobes (e.g., due to the distribution of gamma-band-generating GABAergic interneurons) or to projections of the auditory cortex to different lobes (Tada et al., 2021).

Cortical gamma oscillations are induced by synaptic interactions between fastspiking parvalbumin-positive  $\gamma$ -aminobutyric acid (PV+ GABA) interneurons and glutamatergic pyramidal neurons (Gonzalez-Burgos and Lewis, 2008). Once triggered by glutamatergic N-methyl-D-aspartate (NMDA) receptors, GABAergic interneurons create postsynaptic potentials and engage in continuous reciprocal inhibition and a recurrent feedback loop (Cohen et al., 2015). Thus, glutamatergic excitation and GABAergic inhibition interact to maintain the E/I (excitation-inhibition), balance disturbances in which are thought to underlie the main symptoms of schizophrenia and autism (Gao and Penzes, 2016). Furthermore, appropriate levels of GABAergic (particularly those of PV+ fast-spiking interneurons) and glutamatergic neurotransmission are essential for normal gamma-band synchronisation and cortical information processing (Coyle, 2012; Ferguson and Gao, 2018; Lee et al., 2015).

Studies on various GABA and NMDA active substances show the role they play in the generation of gamma-band ASSR. Ketamine, which is a GABA agonist and NMDA antagonist that induces schizophrenia-related abnormalities, has been shown to enhance ASSR phase-locking at different frequencies in awake rats after a single dose (Vohs et al., 2012). The same results were obtained with a single dose of MK-801 (Sullivan et al., 2015) and phencyclidine (PCP) (Leishman et al., 2015), which are also NMDA antagonists and induce a psychotic behaviour both in rats and humans. 40 Hz ASSR studies in schizophrenic and healthy subjects show that NMDA hypofunction leads to inadequate fast-spiking of cortical GABAergic interneurons (Gonzalez-Burgos and Lewis, 2008; Tada et al., 2016). Furthermore, in schizophrenia patients, an association was found between gamma-band ASSR and the relative plasma levels of d-serine, an NMDA receptor co-agonist, a finding that suggests a pathogenic mechanism involving the NMDA receptor (Koshiyama et al., 2019). Overall, these studies provide convincing evidence that gamma-range ASSR is a sensitive biomarker of GABAergic-glutamatergic balance, that is, E/I balance associated with abnormal gamma activity, which is observed in neuropsychological disorders with symptoms of impaired cognitive function.

However, acetylcholine (ACh) neurotransmitters can also affect gamma range ASSR. Some data propose that the cholinergic projections from the basal forebrain that are extensively distributed to the cortex and thalamic nuclei may be implicated in the regulation of ASSR by attention (Roberts et al., 2013). Additionally, cholinergic projections to the subcortical auditory pathway may alter the cortical ASSR (Harkrider and Champlin, 2001; Zhang

et al., 2016). Thus, ASSR disorders may also reveal some changes in cholinergic transmission.

#### 2.2.4 Stimuli for evoking ASSR

Different types of stimuli are used to induce ASSR: clicks or tone-bursts, chirps, amplitude (AM) or frequency modulated (FM) tones.

**Click stimuli** are short but broad-band frequency spectrum sound stimuli. The most commonly used click stimuli are repeated brief noise bursts or short square stimuli (Laukli and Burkard, 2015). However, due to the cochlear travelling wave delay caused by the distribution of high- to low-frequencies perception from base to apex in the cochlea, when a transient stimulus such as a click is used, the response of the nerve fibres in the basal region of the cochlear partition precede activity in the apical region by several milliseconds (Elberling et al., 2010). Thus, the response excites nerve fibres not simultaneously.

**Amplitude modulated (AM) tones** are created by temporally modulating a tone (sinusoid) with another sine wave, so the amplitude of the tone changes over time. The carrier frequency is the fundamental frequency of the tone, while the modulation frequency is the fundamental frequency of the modulation envelope (Jackson and Moore, 2013). The most common tone used to elicit ASSR is the sinusoidal-amplitude-modulated (SAM) tone. SAM ( $s_I(t)$ ) is calculated as follows:

$$s_1(t) = a sin(2\pi f_c t)(1 + m_a cos(2\pi f_m t))$$
(2.1);

where t is the time course,  $m_a$  is the modulation depth,  $f_c$  is the carrier tone frequency, and  $f_m$  is the envelope modulation frequency.

**Frequency modulated (FM) tones** are produced when the fundamental tone frequency is varied at a particular rate within a range determined by the modulation index. While both AM and FM stimuli activate the same brain regions, AM stimuli result in higher total auditory activation than FM stimuli (Hart et al., 2003). Mixing both AM and FM results in mixed modulation stimuli: the amplitude-modulated carrier is modulated at a different frequency (Korczak et al., 2012).

**Chirp stimulus** is an increasing frequency stimulus that can be created using an amplitude modulated sinusoidal tone that is modified by linearly increasing the modulation frequency (Artieda et al., 2004) (Fig. 2.3). ASSRs to a chirp stimulus change continuously in amplitude and phase depending on the amplitude and phase of the stimulus modulation envelope, which is why these responses are incorrectly referred to as "steady-state responses" and are called "envelope-following responses" (Artieda et al., 2004; McFadden et al., 2014; Purcell et al., 2004). Compared to conventional ASSR, EFRs not only have a larger amplitude (Liu et al., 2019), but also a lower threshold and are statistically more reliable (Lee et al., 2016). EFR allows the simultaneous capture of physiologically relevant activity in the low and high gamma bands, giving a more complete picture of the brain's response (Binder et al., 2020).



**Figure 2.3** Schematic diagram of the chirp stimulus creation. The stimulus can be created using sinusoidal tone, which is linearly modulated by increasing the modulation frequency within a given frequency window (Griškova-Bulanova et al., 2021).

#### 2.2.5 ASSR measures

ASSRs, like standard ERPs, are generated by segmenting the continuous EEG at the onset of the stimulus and then averaging the segments to determine the temporal activity induced by the stimulus. Conventional ASSR analysis techniques are based on Fourier and Wavelet Analysis methods. Both enables the depiction of evoked activity in the time and frequency domains (Herrmann et al., 2004). Time-frequency analysis of EEG signals has traditionally been carried out using the Short-time Fourier Transform (STFT), which calculates Fourier spectra on successive moving windows (Moca et al., 2021). However,

since the product of time and frequency resolution is constant (due to the Heisenberg-Gabor uncertainty principle) and it is not possible to accurately localise the signal in both time and frequency simultaneously, a constant window STFT cannot capture events of different durations (Moca et al., 2021). The wavelet transform decomposes the signal not into a simple sinusoid of infinite length, as in the case of the Fourier transform, but into wavelets of small duration derived from a single prototype wavelet, called the mother wavelet, by applying dilatations and contractions and displacements (Akin, 2002). The Morlet wavelet transform is commonly used to analyse the temporal frequency, instantaneous power and phase of an EEG signal. The common Morlet wavelet transform has a different time and frequency resolution at each scale: if the wavelet's number of cycles is maintained fixed, the temporal width varies as a function of the frequency, and thus the temporal resolution of a wavelet is better at higher frequencies than at lower frequencies (Handy, 2005). This is particularly useful when investigating higher frequency oscillations such as the gamma-range of the EEG.

Isolated power values are often assessed at the maximum frequency of the ASSR (Roach et al., 2019a). The ASSR power measurements are classified into (1) stimulus-evoked measures the average power of the ASSR oscillations that are phase-synchronised with the stimulus, (2) total power is the average power of all oscillations, and (3) the baseline power (resting-state power) is residual, stimulus-independent power (Mathalon and Sohal, 2015). In order to calculate the evoked power, the EEG signal is averaged over the trials and subjected to time-frequency analysis (Mathalon and Sohal, 2015). In contrast, to obtain the total power, each trial is time-frequency decomposed to obtain power, which is averaged over all trials (David et al., 2006). Decomposing the time and frequency of individual trials, e.g., using STFT, helps to estimate the power of a single test in order to calculate total power (Vohs et al., 2012). When the evoked power is subtracted from the total power, the base power is obtained (Tallon-Baudry et al., 1996). Examining baseline power is essential when using realistic dynamic stimuli since sensory information continuously unfolds and is not necessarily phase-locked to stimulus onset (Gao et al., 2021). The average power deviation from the baseline, called the event-related spectral perturbation (ERSP) (Delorme and Makeig, 2004). Since the ERSP does not take into account the potential of event-related phase resetting, it is advisable to use simultaneous phase measurements (Makeig et al., 2004).

ASSR temporal correlations are best evaluated in terms of the phase of the oscillations using a measure such as a phase-locking index (PLI), also referred to as inter-trial phase coherence (ITPC) (Sazonov et al., 2009). PLI gives information on the phase consistency of the response at a specific frequency (Roach and Mathalon, 2008). To obtain the PLI, STFT or complex Morlet wavelet analysis is performed to determine the variation in amplitude and phase angle with time. The complex output is divided by its complex norm and averaged across trials, revealing normalised PLI. The PLI value may vary from 0 (no synchronisation) to 1 (perfect synchronisation across trials at a given latency) (Roach and Mathalon, 2008). Thus, PLI reflects the temporal stability of oscillatory activity at particular locations from trial to trial. Low phase synchronisation is linked to higher spatial differentiation of potentials (Thatcher et al., 2005). PLI measurements are more reliable than evoked power measurements (McFadden et al., 2014). Additionally, with the PLI, a time-frequency measure known as the phase-locking angle (PLA) also could be used (Roach et al., 2019a, 2019b). PLA is a measure of the deviation of the phase angles of the oscillations recorded at a given frequency compared to a reference sample (e.g., a healthy control group) (Roach et al., 2019b). Compared to power or PLI measures, PLA measures are more sensitive to differences in patient and control group characteristics (Roach et al., 2019b).

The more encompassing whole-brain ASSR measure is global field synchronisation (GFS) (Griškova-Bulanova et al., 2018; Koenig et al., 2012). The GFS estimates the extent to which all channels are phase-aligned at a given frequency, without making any assumptions about the spatial location of activity (Koenig et al., 2005). EEG signals are first converted into frequency domains, and the signals at each frequency are then mapped onto a complex 2-D plane. The GFS value of a frequency is defined as the normalised difference between the two eigenvalues of the covariance matrix along the two vectors (sine and cosine coefficients) (Jalili et al., 2013). If the sets of sine and cosine values form a line, one of the eigenvalues is equal 0, and a principal component fully describes the covariance — the GFS is equal to 1. This means perfect phase synchronisation. In the absence of phase synchronisation, the two eigenvalues are close toward one other, resulting in GFS values close to zero: this implies that the entries are equally loaded on both principal components and that no preferred phase can be identified (Koenig et al., 2001).

#### 2.2.6 Temporal dynamics of ASSR

During the first 100 ms after auditory stimulus onset, a transient GBR emerges, comparable to the response elicited by the onset of any noise burst (Rojas et al., 2011). GBR is sometimes called the early-latency response, which occurs in the primary and secondary auditory cortices (Pantev, 1995).

After 100 ms from stimulus onset, the amplitude of the 40 Hz ASSR develops and grows linearly until it reaches a peak at 250 ms, when steady-state response (also termed a late-latency response, lasting between 250-500 ms) occurs (Roach et al., 2019a). Between this time point and the end of the stimulus, a steady-state response shows the consistent 40 Hz amplitude (Roach et al., 2019a). The ASSR fades only within 50 ms after the stimulus offset (Popov et al., 2018).

It was shown that distinct brain circuits contribute to the ASSR at early and late latencies and that these ASSR components are impacted differentially by endogenous and exogenous variables (Griškova-Bulanova et al., 2016; Li et al., 2013). The early response involves early sensory processing, while during late-latency steady-state response a task-specific neuronal population is activated (Li et al., 2021; Roach et al., 2019a; Saupe et al., 2009b). In addition, each response has a different generator in the primary auditory cortex (Pantev et al., 1993; Roß et al., 2002), and the late-latency response contains additional subcortical generators, such as bilateral posterolateral cerebellar hemispheres (Farahani et al., 2021). Finally, early- and late-latency ASSRs differ between clinical stages of schizophrenia: early-latency ASSRs are associated with clinical symptoms in ultra-high-risk schizophrenia, whereas late-latency ASSRs are associated with large variations in clinical symptoms and attentional performance in patients with first-episode schizophrenia (Tada et al., 2016). In schizophrenia patients, gamma-band ASSR deficits in the superior temporal gyrus during the early response, followed by widespread disruption of interactions between prefrontal brain regions during the late response (Koshiyama et al., 2020a).

#### 2.2.7 Individual gamma frequency

The individual gamma frequency (IGF) may be estimated using either conventional single-frequency stimulation or periodic stimulation with a wide variety of stimulation frequencies such as chirps. In the latter case, the ASSR follows the envelope of the chirp stimulation waveform, covering a wide window of frequencies within a single oscillation (Purcell et al., 2004), with the peak of the IGF manifesting as the envelope frequency response (EFR) (Griškova-Bulanova et al., 2021; Purcell et al., 2004). The peak amplitude of the EFR is usually around 40 Hz, with a sharp drop in amplitude above 50 Hz (Miyazaki et al., 2013) and while the peak frequency varies between subjects, its amplitude and frequency are relatively constant (Zaehle et al., 2010). Moreover, in the 30-60 Hz range, phase-locked activity is highly correlated

with IGF (Gransier et al., 2021). Gransier et al. (2021) hypothesised that the ASSRs recorded in the 30-60 Hz range are generated by the same oscillators and that relative measurements are not influenced by stimulation frequency. This hypothesis is supported by similar IGF topographies and recent studies in clinical populations using chirp stimulation: (1) hallucination scores in patients with schizophrenia and PLIs of ASSRs are associated within the 32-43 Hz frequency range (Griškova-Bulanova et al., 2021), and (2) clinical assessment results in individuals with impaired consciousness are associated with response to chirps within the 38-43 Hz frequency range (Binder et al., 2020, 2017).

The IGF assessment is particularly useful in clinical trials as it allows for a quick assessment of the individual characteristics of networks involved in responses, which may be related to cognitive abilities (Griškova-Bulanova et al., 2021). Studies have also provided evidence that frequency variation within the gamma range is also related to perception (i.e., the ability to detect small and sudden changes in sound stimuli) in healthy subjects (Ross and Pantev, 2004; Baltus et al., 2018; Ross and Pantev, 2004). In summary, and given that the preferred oscillation frequencies of networks are influenced by their anatomical and functional properties, such as the time constants of synaptic connections, e.g., glutamatergic or GABAergic (Traub et al., 1997; Whittington et al., 2000), and the rate of transmission of the neurons (Hutcheon and Yarom, 2000; Izhikevich et al., 2003), IGFs may be able to reflect the properties of the individual networks more accurately than the more commonly used ASSRs at 40 Hz.

#### 2.3 Factors affecting ASSR

#### 2.3.1 Gender impact on ASSR

Female ASSRs have been found to have earlier latency and higher amplitude than males (Zakaria et al., 2016). However, another study showed that the influence of gender on ASSR is not so obvious: the difference in 40 Hz ASSR phase-locking and intensity between the genders is significant in the left-handed group (lower in the female group), whereas there no difference in the right-handed group (Melynytė et al., 2018). The results show that gender is not the only factor influencing 40 Hz ASSR, but rather a combination of gender and hand. Another study, by Girskova et al. (2014), found that ASSR in women depends on the menstrual cycle. ASSR amplitude and phase-locking values increased linearly with increasing 17-oestradiol levels, with the

highest estimates obtained in the late follicular phase and the lowest in the mid-luteal phase (Griškova et al., 2014).

#### 2.3.2 Age-related ASSR changes

Studies on age-related changes in ASSR are relatively few and inconclusive. During childhood and adolescence, the amplitude of ASSR increases steadily with age (Aoyagi et al., 1994; Ono et al., 2020; Herdman, 2011; Poulsen et al., 2009; Rojas et al., 2006; Edgar et al., 2016). The 40 Hz ASSR increases especially from late childhood to early adolescence (8-13 years) (Cho et al., 2015). Rojas et al. (2006) described the change in 40 Hz ASSR power with age between 5 and 20 years as an increasing exponential regression (Rojas et al., 2006). However, around the age of 20-22 years, the ASSR decreases (Cho et al., 2015; Edgar et al., 2014).

Studies of adults at different ages have shown conflicting results: some have found that age has no effect on ASSR (Boettcher et al. 2001, Rojas et al., 2006), others have found that ASSR amplitude increases with age (Puolsen et al., 2007), and still others have found that ASSR amplitude declines with age (Griškova-Bulanova et al., 2013; Thuné et al., 2016). Poulsen et al. (2007) showed that between 19 and 45 years of age, the ASSR becomes larger and more stable, with the peak of the IGF increasing from 38 Hz to 46 Hz (Poulsen et al., 2007). However, Griškova-Bulanova et al. (2013) showed that the 40 Hz ASSR PLI and the induced amplitude decrease with age, as seen in subjects aged 20-60 years. In addition, Thuné et al. (2016) meta-analysis revealed that the decline in ASSR with age is particularly pronounced in patients with schizophrenia (Thuné et al., 2016). Thus, the results suggest that the 40 Hz ASSR varies with age, but studies on age-related changes in ASSR are quite controversial.

#### 2.3.3 ASSR relationship to arousal state and attention

Arousal and attentiveness are two interdependent psychological processes (Storbeck and Clore, 2007). The arousal state is defined as non-specific activity in the cerebral cortex associated with the transition between sleep and wakefulness; it is thought to influence the ability of sensory and neural circuits to synchronise at gamma frequencies (Griškova et al. 2007). Attention, on the other hand, refers to the focusing of task-related energy, given the baseline level of energy and arousal during the task, and involves a more goal-directed

activity of the cerebral cortex that facilitates information processing (Barry et al., 2005).

Linden et al. (1987) studied the effect of attention on the 40 Hz ASSR by comparing response amplitudes under two conditions: when attention is focused on the stimulus and when no attention is paid to the stimulus (reading text) (Linden et al., 1987). However, early experiments on attentional modulation of ASSR were unsuccessful, and Linden et al. (1987) concluded that there is no evidence that attention affects ASSR. But more recent studies have shown that attention increases ASSR in contralateral auditory cortical areas (Bharadwaj et al., 2014; Lazzouni et al. 2010; Müller et al. 2009) and by an average increase of 14% in the total ASSR power (up to 80% in the frontal areas, and 20% to 25% in temporal and parietal cortices) (Manting et al., 2021). However, the results of studies on the effects of attention on ASSR are more complex when comparing different attentional states. The highest global field synchronisation (GFS) of 40 Hz ASSR is obtained both when participants are directly focusing on the stimulus (counting the stimuli) and when they are relaxing with their eyes closed and letting their mind wander, compared to the ASSRs obtained during distraction condition (reading the text silently) (Griškova-Bulanova et al., 2018). 40 Hz ASSR decreases with increasing cognitive load (Yokota et al., 2017; Yokota and Naruse, 2015). Therefore, the current literature is inconsistent on how the ASSR is influenced by selective attention.

Regarding the modulation of the 40 Hz ASSR depending on the state of arousal, the 40 Hz ASSR is generally higher at lower states of arousal. This has been shown in studies where subjects had to sit with their eyes closed or do some reading: ASSR was higher during the eyes-closed condition (Griškova et al., 2007, 2009). Similarly, in another study, subjects in a relaxation state induced by a small amount of alcohol combined with the absence of external stimuli also produced larger ASSRs (Pockett and Tan, 2002). In contrast, ASSR is reduced during sleep. This reduction is not only at 40 Hz (Górska and Binder, 2019; Haghigih and Hatzinakos, 2014; Lustenberger et al., 2018), but also at all frequencies from 5 to 80 Hz (Tlumak et al., 2012). ASSR amplitudes decrease more during the N2 and N3 phases of sleep than during rapid eve movement (REM) sleep (Picton et al., 2003b). However, rhythmic sounds used during non-rapid eye movement (NREM) sleep not only induce ASSR, but also increase spindle activity during and shortly after tone presentation. At the same time the activity of delta waves, also known as slow waves, is increased and the 40 Hz PLI is significantly reduced (Lustenberger et al., 2018).

ASSR in schizophrenia. Schizophrenia is associated with alterations in ASSR over a wide range of frequencies: lower ASSR values have been found between 2.5 Hz and 80 Hz stimulation (Hamm et al., 2011; Parker et al., 2019; Puvvada et al., 2018; Tsuchimoto et al., 2011). However, studies have shown that schizophrenia leads to a reduction in ASSR power and PLI, mostly at 40 Hz (Thuné et al., 2016; Kwon et al. 1999). A meta-analysis of 14 phase and 15 power experiments confirmed the consistency of this phenomenon (Thuné et al. 2016). It has also been found that in schizophrenia, the 40 Hz ASSR is slightly asymmetric in the different hemispheres, with a predominance of the right hemisphere, and in schizophrenic patients, the right ASSR is lower than the left (Tsuchimoto et al., 2011; Ross et al., 2005). MEG analysis revealed a reduction in 40 Hz ASSR amplitude in the right Heschl's gyrus, right thalamus and right hippocampus patients with first-episode psychosis or in participants at or clinical high-risk psychosis (Grent-'t-Jong et al., 2021). In addition, 40 Hz ASSR PLI correlates positively and power correlates negatively with grey matter volume in the left Heschl's gyrus in chronic schizophrenic patients (Hirano et al., 2020). These results regarding Heschl's gyrus are not surprising as it is located in the primary auditory cortex and schizophrenia is characterised by a reduction in its grey matter, especially in the left hemisphere (Takahashi et al., 2009).

Moreover, in individuals with psychotic disorders, ASSR is associated with symptom severity and global functioning (Zhou et al., 2018; Grent-'t-Jong et al., 2021). Early latency ASSR measurements negatively correlated with ratings of negative symptoms on the Positive and Negative Syndrome Scale (PANSS) (Griškova-Bulanova et al., 2016). In addition, a positive correlation has been found between 40 Hz ASSR PLI in the left auditory cortex and the presence of positive auditory hallucinatory symptoms (Spencer et al., 2009). The persistence of attenuated psychotic symptoms and transition to psychosis can be predicted by 40 Hz ASSR disturbances in the right hippocampus, superior temporal gyrus, and middle temporal gyrus in individuals with clinically high-risk psychosis (Grent-'t-Jong et al., 2021).

Reductions in 40 Hz ASSR phase-locking have already been observed in schizophrenic patients hospitalized for a first episode of psychosis and individuals at clinical high risk (Tada et al., 2016; Spencer et al., 2008) as well as in adolescents diagnosed with a psychotic disorder (Wilson et al., 2008). In addition, a lower ASSR of 40 Hz has been found in previous studies in first-degree relatives (Hong et al., 2004; Rass et al., 2012) and in individuals with the 22q11.2 deletion syndrome, who do not develop a psychotic disorder but

are at a substantially higher risk of developing schizophrenia (Larsen et al., 2019, 2018). Thus, ASSR disorders may be a premorbid risk factor for schizophrenia. In contrast, individuals with schizotypal personality disorder, which is phenotypically similar to schizophrenia in terms of cognitive impairment, neurobiological abnormalities and familial risk, have typical and unaffected 40 Hz ASSR, suggesting that these disorders do not have a shared pathophysiology with schizophrenia (Rass et al., 2012).

ASSR in bipolar disorder. Although ASSR gamma band oscillations have received less attention in bipolar disorder than in schizophrenia, it has been observed that bipolar disorder is also characterised by a decrease in ASSR power (Onitsuka et al., 2013). Similar to schizophrenia, the 40 Hz ASSR shows reduced asymmetry between the left and right hemispheres of the primary cortex (Reite et al., 2009). Using MEG, it has been found that bipolar disorder patients have a lower 40 Hz ASSR on the right side (Maharajh et al., 2007; O'Donnell et al., 2004), in both manic and mixed states (O'Donnell et al., 2004), and also during the first hospitalization and in the chronic state (Oda et al., 2012; O'Donnell et al., 2004; Rass et al., 2010). In unmedicated bipolar patients, ASSR power and PLI are lower at 40 Hz, also at 20, 30, 50 and 80 Hz (O'Donnell et al., 2004; Parker et al., 2019; Rass et al., 2010; Spencer et al., 2008). However, 40 Hz ASSR in bipolar disorder has been suggested as a potential biomarker useful in distinguishing bipolar disorder from major depressive disorder, as it has been found that patients with major depressive disorder do not show significant differences in 40 Hz ASSR power or phase-locking when compared to healthy subjects (Isomura et al., 2016). Conversely, as patients with schizophrenia and bipolar disorder have similar ASSR impairments, this suggests that both disorders share the same neural circuitry impairments (Sugiyama et al. 2021).

**ASSR in neurodegeneration diseases.** Individuals with dementia or moderate cognitive impairment have a strong correlation between pure tone audiometry and ASSR thresholds (Villeneuve et al., 2017). Despite the large differences in ASSR threshold across frequencies in healthy individuals, the 40 Hz ASSR threshold in the AD group is similar to the 80 Hz ASSR threshold (Shahmiri et al., 2017). The lack of differences between thresholds may be related to insufficient cortical response to 40 Hz frequency and neurodegeneration of the temporal lobe (Villeneuve et al., 2017). However, reduced cortical inhibition in Alzheimer's disease results in an increase in 40 Hz ASSR power, which increases further as the disease progresses (Herrmann et al., 2004; van Deursen et al., 2011; Osipova et al., 2006).

Studies on ASSR in multiple sclerosis are scarce. Gamma-band somatosensory evoked potentials in multiple sclerosis patients show a

significant decrease in the phase-locking values between primary and secondary somatosensory cortex (Hagiwara et al., 2010). Multiple sclerosis patients with cognitive impairment have a lower peak gamma band response frequency (IGF EFR) compared to patients without cognitive impairment and control subjects (Arrondo et al., 2009).

ASSR in autism spectrum disorders. Typically developing people show a significant decrease in gamma power with age, whereas people with ASD do not (Ono et al., 2020). Conversely, the PLI of ASSR decreases with age in ASD individuals (aged 6-25 years), becoming significantly lower than in typically developing individuals (De Stefano et al., 2019). This interaction between age and diagnosis suggests that typically developing and ASD patients have different developmental trajectories for low gamma power (De Stefano et al., 2019). Furthermore, the sustained deflection of the 40 Hz magnetic field during ASSR is moderately reduced, significantly delayed and shifted to the left hemisphere in children with ASD aged 7-12 years, irrespective of their cognitive level or degree of autistic symptoms (Stroganova et al., 2020). Studies in the adolescent population (aged 14-20 years) have also found reduced GBR in individuals with ASD (Seymour et al., 2020). Notably, adolescents with ASD show an increase in 40 Hz ASSR PLI after treatment with the GABA-B agonist STX-209 (arbaclofen) (Roberts et al., 2019). The results in first-degree relatives of autistic individuals are consistent with an inherited endophenotype of neural synchrony: in both hemispheres, 40 Hz ASSR evoked power and PLI are lower compared to controls, not only in autistic patients (Seymour et al., 2020), but also in their parents (Rojas et al., 2011). On the other hand, Edgar et al. (2016) and Stroganova et al. (2020) found no differences in ASSR between ASD and control groups in their studies.

**ASSR in dyslexia.** Impaired gamma-band ASSR has been observed in school-aged children and adults with dyslexia (Lehongre et al., 2011; Lizarazu et al., 2015; Van Hirtum et al., 2019). In dyslexia, inadequate processing of rapidly changing auditory information is thought to lead to underdevelopment of phonological representations, leading to reading and spelling problems (Poelmans et al., 2012). At 20 Hz ASSR, which corresponds to the phoneme processing frequency, phase coherence, including intrahemispheric and interhemispheric coherence, has been found to differ between normal-reading adults and adults with dyslexia (Poelmans et al., 2012; Vandermosten et al., 2013). Other studies have found that in control groups, ASSRs of 25-35 Hz are dominant on the left side of the planum temporale, while in dyslexic subjects ASSRs are absent or have reverse asymmetries, which can impair the representation of or access to phonemic units (Lehongre et al., 2013, 2011;

Poelmans et al., 2012). In children later diagnosed with dyslexia, 80 Hz ASSR in the right temporoparietal and occipital regions was significantly lower during pre-school reading (Gransier et al., 2021), but no differences in phoneme-frequency (20 Hz) neuronal synchronisation were found by researchers before the acquisition of reading skills (De Vos et al., 2017). Transcranial alternating current stimulation (tACS) at a frequency of 30 Hz can enhance the ASSR on the left side, which improves phonological skills in individuals with dyslexia (Marchesotti et al., 2020).

#### 2.3.5 ASSR and cognitive functions in neuropsychiatric conditions

In previous studies examining the relationship between gamma-range ASSR and cognitive processes, ASSR has mainly been assessed in clinical populations using tasks involving a range of cognitive processes. Gamma-range ASSR has been found to be associated with cognitive flexibility and reasoning in healthy study participants, as measured by complex tasks such as the Similarities (WAIS-III; Wechsler, 1997) (Rass et al., 2010) and the Mazes test (MCCB; Nuechterlein et al., 2008) (Sun et al., 2018). Further, ASSR is associated with behavioural indicators of processing speed, i.e., performance on the Trial Making Test (MCCB; Nuechterlein et al., 2008) (Sun et al., 2018) and Symbol Coding (WAIS-III; Wechsler, 1997) (Rass et al., 2012).

ASSR and cognitive functions in schizophrenia. Studies examining the relationship of gamma-range ASSR with cognitive performance in patients with psychotic symptomatology have found that higher ASSR is associated with better performance on tasks requiring short-term memory (Light et al, 2006; Puvvada et al., 2018), fast access to long-term/semantic memory (Kim et al., 2019), and performance on simple reaction time tasks (Tada et al., 2016). However, performance on complex reasoning tasks is inconsistent (Rass et al., 2012; Sun et al., 2018), and some studies in individuals with psychotic symptoms have found no association between gamma-range ASSR and cognitive outcomes (Bartolomeo et al., 2019; Hirano et al., 2020; Kirihara et al., 2012; Leonhardt et al., 2020; Murphy et al., 2020). Interestingly, Molina et al. (2020) found that baseline ASSR predicted improvements in cognitive function after cognitive training with auditory tasks, suggesting that improved ability to maintain gamma oscillations may be the neural mechanism by which cognitive training improves cognitive function (Molina et al., 2020).

**ASSR and cognitive functions in bipolar disorder.** Only Rass et al. (2010) conducted a study of associations between ASSR and cognitive abilities in bipolar patients, but found no correlations between ASSR and
cognitive performance as measured by several subtests of the WAIS-III (Wechsler, 1997).

**ASSR and cognitive functions in neurodegeneration diseases.** Multiple sclerosis patients who perform better on several cognitive tasks from the Brief Repeatable Battery Neuropsychological (BRB-N; Rao 1990) tests have higher IGF (Arrondo et al. 2009). In patients with Alzheimer's disease, 40 Hz ASSR correlates with better overall functioning as assessed by the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) (van Deursen et al., 2011).

ASSR and cognitive functions in autism spectrum disorders. Approximately 170 ms after the stimulus, ASSR power in the right transverse temporal lobe at 30 Hz is higher in subjects with ASD than in normally developing subjects (Ono et al., 2020). However, a correlation between the Kaufman Assessment Battery for Children (K-ABC; Kaufman and Kaufman, 1983) simultaneous processing score and the left 40 Hz ASSR response was found in both the typically developing and ASS groups (Ono et al., 2020).

**ASSR and cognitive functions in dyslexia**. Studies assessing language skills in dyslexic individuals have found a negative correlation between gamma-range ASSR and phonological awareness and fluency, literacy and non-word repetition (Lehongre et al., 2011; Van Hirtum et al., 2019). These results are consistent with the relationships between ASSR and performance on speech recognition ability tasks (Alaerts et al., 2009; Leigh-Paffenroth Fowler, 2006).

### 2.4 Cognitive functions

Cognitive functions<sup>\*</sup> are a range of mental abilities<sup>\*\*</sup>, including learning, thinking, reasoning, remembering, problem solving, decision-making and attention (Fisher et al., 2019). Cognitive performance is usually described in terms of separate cognitive domains (Harvey, 2019; Agrawal et al., 2020). Each domain usually contains further subdomains related to processes in areas of the brain (Agrawal et al., 2020). Cognitive domains can be conceptualised in a number of ways: (1) hierarchically, with more fundamental sensory and

<sup>\*</sup> Function – the action for which a thing is specially fitted or used or for which a thing exists (Merriam-Webster; retrieved retrieved 22/03/2022).

<sup>\*\*</sup> Ability – competence in doing something (Merriam-Webster; retrieved 22/03/2022).

perceptual processes at the bottom and more complex functions at the top (D'Mello et al., 2020), and (2) according to the localisation in the brain where these processes occur (Engelhardt, 2019). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), identifies six main domains of cognitive function: complex attention, executive functions, learning and memory, language, perceptual and motor functions, and social cognition, each with its own subdomains (American Psychiatric Association, 2013). Although there is broad agreement on the basis of most of these categories, there is some inconsistency in the clinical and scientific literature, as noted in the Harvey review (2019).

Neuropsychological assessment is the basis of the clinical approach used to diagnose and evaluate the treatment of cognitive impairments. As a result, many neuropsychological measures have been developed to address each cognitive subdomain (Casaletto and Heaton, 2017). Tasks often require the coordination of a variety of sensory, perceptual, attentional and other more or less complex processes, while basic sensory tasks involve only minimal basic higher-level processing (Elwood, 2001; Eramudugolla et al., 2017). A commonly used measure of intelligence and specific cognitive abilities is the Wechsler Adult Intelligence Scale (WAIS; first version Wechsler, 1955). It is translated, adapted and standardised in dozens of countries around the world (O'Connor and Ammen, 2013). The current version of the test is the Fourth Edition (WAIS-IV; Wechsler, 2008). It comprises a Full-scale IQ, as well as indexes on four factors: Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed. Another tool used to design, conduct and share cognitive tests is the Psychology Experiment Building Language (PEBL), a free, open-source software system that allows researchers and clinicians to manage the presentation of stimuli, the collection of responses and the recording of data (Mueller and Piper, 2014). Part of the PEBL package, which is currently consisting of more than ninety tasks, has been used in the development of PEBL-Lt - cognitive tasks translated, modified or created in Lithuanian and questionnaires designed to measure information processing and factors related to it (Jurkuvenas, 2015). However, some other methods of measuring cognitive abilities are more appropriate for patients based on their disorder. The MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008) and Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004) were developed as an assessment tool for schizophrenia clinical trials. The Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog; Mohs et al., 1983) is a commonly used measure for assessing cognitive dysfunction in patients with Alzheimer's disease. These are only a few examples of tools for assessing cognitive skills.

Cognitive tasks allow an objective and standardised assessment of an individual's cognitive skills and impairments, indirectly providing information about the anatomical and functional integrity of brain regions and networks (Canevelli et al., 2019; Casaletto and Heaton, 2017).

### 2.4.1 Global cognition or intellectual ability (g)

The Cattell-Horn-Carroll (CHC) theory of cognitive abilities is the most comprehensive and empirically valid psychometric theory of the structure of cognitive abilities (Flanagan and Dixon, 2014). As CHC theory is based on a large body of empirical evidence in the scientific literature, it is actively used in the selection, organisation and interpretation of tests of intelligence and cognitive ability (Reynolds and Fletcher-Janzen, 2007). CHC theory describes a hierarchical system of cognitive abilities, which are differentiated according to the level of generality: narrow abilities (stratum I), broad abilities (stratum II) and g (stratum III) (Fig. 2.4).



**Figure 2.4** Carroll's Three Stratum Model of Human Intelligence: General intelligence (g) fluid intelligence (Gf), crystallized intelligence (Gc), general memory and learning (Gy), broad visual perception (Gv), broad auditory perception (Gu), broad retrieval ability (Gr), broad cognitive speediness (Gs), and processing speed (Gt).

Narrow skills are approximately 70 limited and specialised skills. Broad abilities include fluid reasoning, crystallized intelligence, short-term memory, visual processing, auditory processing, long-term storage and retrieval, processing speed, reading and writing, quantitative knowledge, and reaction

time/decision speed, with g at the top of the hierarchical model (Floyd et al., 2007). The g-factor (also known as general factor, general mental ability or global cognition) is the factor that determines the performance of all cognitive tasks – regardless of the task, if it requires intellectual ability, it requires g; the second factor is test-specific (Sternberg, 2012).

The g-factor emerged from empirical evidence showing that scores on various cognitive tests are positively correlated in the population, i.e. individuals who score above the population mean on any test tend to score above the mean on average, while those who score below the mean on all other tests tend to score below the mean on any test on average (Bock et al., 2003). g is highly stable across different factor analysis algorithms, different test batteries and different samples (Jensen, 2000).

As g is not an absolute measure (it is norms-based, i.e. the results are relative to the particular group of people from which they were obtained) (Jensen, 1992), most studies use global cognitive measures, such as the IQ of the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955). The ranking of a subject's g-factor scores usually correlates strongly with the ranking of his/her IQ scores on conventional intelligence tests (Colom et al., 2006). However, IQ is the sum of standardised scores, and therefore IQ depends on both g and a combination of specific cognitive abilities and skills (Colom et al., 2002). Still, composite measures of global cognition made up of several different cognitive tests have the advantages of reducing the number of outcome measures to a more acceptable level, allowing better detection of change, being more sensitive to disease state and treatment effects in small samples (Shwartz et al., 2015; Malek-Ahmadi et al., 2018). Nonetheless, global cognition assessment does not reflect specific effects on particular cognitive functions (Weintraub et al., 2018).

## 2.4.2 Executive functions

Executive functions are a group of top-down mental processes that are needed to function in more complex situations where automatic actions are inappropriate or impossible by enabling individuals to regulate their thoughts and actions during goal-directed behaviour (Diamond, 2013; Friedman and Miyake, 2017). There is much debate as to whether executive functions should be seen as a single construct or as several separate functions, but many argue that it is best to think of executive functions as separate functions with some links between them (McCabe et al., 2010). It is generally agreed that there are three main executive functions: (1) inhibitory control and selective

attention, (2) working memory (maintaining and updating information) and (3) cognitive flexibility (set-shifting) (Diamond, 2013). Due to the complex nature of executive functions, many of the tasks used to assess executive functions, such as the Wisconsin Card Sorting Test (WCST; Berg, 1948), the Trail-Making Test (TMT; Reitan, 1955), the Semantic Word List Generation (WLG; Rao, 1990) and Tower of London (ToL; Shallice, 1982), also have a complicated underlying structure because they require the interaction of different cognitive skills (Karr et al., 2018). Research on these tasks has revealed complex and distributed networks of brain regions active in executive tasks: the frontoparietal network (includes the bilateral inferior or middle frontal gyrus, dorsolateral prefrontal cortex (DLPFC), inferior parietal lobule, superior parietal lobule, and pre-motor areas) and the cingulo-opercular network (includes the dorsal anterior cingulate cortex and bilateral anterior insula) (Engelhardt et al., 2019; Newman et al., 2009; Nitschke et al., 2017).

# 2.4.3 Information processing speed

Information processing speed is a measure of cognitive performance that indicates how fast information is perceived, understood and acted upon (Dehn, 2006; Silva and Lee, 2021). Research in cognitive psychology and developmental psychology has shown that the information processing speed is crucial for all other cognitive processes: an increase in processing speed correlates with an increase in working memory capacity, which in turn leads to an improvement in complex reasoning (Kail et al., 2016; Koekkoek et al., 2014). The information processing speed is also not related to specific area of the brain, but probably depends on the integrity of the entire brain network, such as white matter (Oschwald et al., 2019). In addition, studies have shown that processing speed is a more relevant indicator of neurophysiological functioning than other cognitive abilities – it is a key indicator of pathological and age-related changes (DeLuca and Kalmar, 2007; Finkel et al., 2009). However, studies using principal component factor analysis have identified two different forms of information processing speed - simple and complex information processing speed (Chiaravalloti et al., 2003). Simple processing speed refers to the speed of basic perceptual evaluation, while complex processing speed involves higher-order cognitive processes (Chiaravalloti et al., 2003). Analysis of the relationship between mental disorders and cognitive abilities has shown that simple information processing speed is more closely related to mental health disorders than to indicators assessing complex abilities (Knowles et al., 2010). This result can be explained by the fact that simple information processing makes it almost impossible to use various strategies, while complex tasks, on the other hand, allow the use of different approaches, which increases the variability of the performance on these tasks and is therefore dependent on the individual's experience (Jurkuvenas, 2016).

# 2.4.4 Cognitive flexibility and reasoning

Cognitive flexibility is an aspect of executive functioning that includes the ability to generate a range of ideas, to consider alternative responses and to change behaviour as circumstances change (Johnco et al., 2013). For cognitive flexibility to be successfully implemented, different areas of executive functions need to work in harmony: firstly, the ability to detect changes in the environment and to focus on those changing elements, as well as the ability to reason, which is used to decide whether a previous strategy is no longer appropriate in a changed environment, and the ability to inhibit previous reactions, as well as to plan and adopt new strategies (Dajani and Uddin, 2015). Reasoning is closely related to cognitive flexibility, as reasoning is the understanding of the abstract relationships between elements in the environment, which enables us to make conscious inferences and apply logical methods to achieve a certain goal (Moshman, 1995). Cognitive flexibility and reasoning is commonly measured in WCST (Berg, 1948), TMT (Reitan, 1955), ToL (Shallice, 1982), and other complex tasks, where it manifests itself as a faster and more accurate perception of the changes in the rules of the task, and a shorter time to plan the next steps (Zhu et al., 2021). The ability of flexibility develops from early childhood through adolescence and adulthood in an inverted-U-shaped trajectory, peaking in the second and third decades of life and declining towards the end of life (Cepeda et al., 2001).

## 2.4.5 Short-term and working memory

Short-term memory reflects the capacity of the human mind to temporarily retain a limited amount of information in a highly accessible state (Cowan, 2008). Short-term memory is easily disrupted unless information is stored in long-term memory – a process called consolidation. However, only a small part of short-term memory is consolidated, and this depends on the level of arousal and attention, which in turn depends on the importance of personal information (Michael-Titus et al., 2010). Studies show that the limit for short-term memory capacity is four items, plus or minus one (Cowan, 2001), and

the amplitude of ERP activity has also been shown to depend on the number of short-term memory items (Vogel and Machizawa, 2004). Short-term memory is supported by separate brain areas: the posterior parietal and anterior frontal networks of the left hemisphere which are more involved in phonological short-term memory, and the right hemisphere, which is more involved in spatial short-term memory (Vallar, 2017).

Working memory refers to the ability to manipulate or otherwise transform information, to protect it from interference, and to use it for highlevel actions such as planning, reasoning and problem solving (Postle and Pasternak, 2009). Working memory encompasses most of the cortex, including the frontal cortex, as well as posterior cortical areas that help maintain specific content (Miller et al., 2018). Evidence suggests that higherorder cortical neurons, including the prefrontal cortex, exhibit a feature of delayed activity - an increased level of firing during delays of workingmemory tasks (Constantinidis et al., 2018; Zylberberg and Strowbridge, 2017). During a short delay of about 1 s, a stimulus to be remembered is presented, this stimulus causes an increase in the number of neuronal firings, and after the stimulus has disappeared, neurons continue to fire, usually at a lower rate but still above the baseline level that preceded the stimulus, thus keeping the stimulus in working memory (Constantinidis et al., 2018; Fuster and Alexander, 1971; Zylberberg and Strowbridge, 2017). Laminar recordings of the frontal cortex show that gamma band activity in the superficial layers reflects active maintenance of working memory (Bastos et al., 2018).

### 2.4.6 Attentional control

Attention is a complex concept involving a number of components: the focused or sustained attention, the selective attention and the shifting attention (Oken et al., 2006; Riccio et al., 2002). Concentrated or sustained attention – the ability to respond discretely to specific visual, auditory or tactile stimuli is considered to be the simplest form of attention, but is important in the early stages of information processing (MacKay-Brandt, 2011). Sustained attention is associated with the cingulo-opercular network, as well as the DLPFC and the inferior parietal lobe, especially in the right hemisphere (Zanto and Gazzaley, 2019). The simplest way to measure attentional fluctuations during sustained attention is instantaneous performance measurement – by studying the trial-to-trial variability of RT, researchers can observe performance fluctuations with high temporal resolution (Esterman and Rothlein, 2019). The focused attention tasks related to target recognition and were administered on

the basis of the Continuous Performance Test (CPT; Cornblatt et al. 1988) – in these tasks, the participant must respond by pressing a key when the target stimulus is presented (Vaughn et al., 2011; Hall et al., 2016).

Selective attention has evolved as the ability to act efficiently in order to achieve a goal, i.e., to divert attention from one aspect of a task in order to be able to perform another effectively (Hommel et al., 2019). The attentional shift observed by non-invasive neuroimaging techniques is related to a mechanism whereby the encoding of task-relevant information is enhanced and the encoding of task-irrelevant information is inhibited (Stevens and Bavelier, 2011; Verghese, 2001). The posterior parietal cortex is the core of the neural basis of selective attention and the main node of the attention network (Corbetta and Shulman, 2011). Selective attention is measured by tasks that involve conflicts between different dimensions of the target stimulus – the ability to resist distraction (Commodari, 2017), e.g., the Stroop task (Stroop, 1935).

### 2.4.7 Language abilities

Language is a shared system of symbols that facilitates communication, categorisation and thinking (Pinker, 2003). Language encourages and allows the expression of flexible cognition: it allows the encoding and publicising of representations of events, entities and relationships, as well as mental states, ideas and intentions (Deak, 2003). Language is usually assessed in terms of receptive vocabulary (comprehension), expressive vocabulary and production, object naming, fluency, reading and writing (Gershon et al., 2013). One of the most widely used tools to test language ability is the WAIS Verbal IQ (Wechsler, 1955), which consists of a series of subtests designed to assess general verbal intellectual abilities: acquired knowledge, verbal reasoning and attention to verbal material (Lange, 2011; Griffiths et al., 2000). Most neuroimaging studies to date have shown that language comprehension, like other complex cognitive tasks, is the result of the interactions of a distributed and tightly interconnected network of neurons, and that the network dynamically reconfigures itself as task demands change (Prat, 2011). The study of the processes involved in language processing identified two distinct pathways in the dorsal brain: one involving Brodmann's area 44 and the posterior superior temporal cortex, which contributes to basic syntactic processing, and another involving the premotor cortex and the superior temporal cortex, which contributes to sensory and motor integration (Berwick et al., 2013). There are also ventrally located pathways that include brain areas that support semantic processing: Brodmann area 45 in the inferior frontal cortex and parts of the temporal cortex (Berwick et al., 2013). Interestingly, skilled language perceivers use fewer neural resources, e.g. proficient language perceivers have significantly lower EEG power in all frequency bands than poor language perceivers (Prat, 2011).

## 2.4.8 Cognitive dysfunctions in neuropsychiatric conditions

**Cognitive dysfunctions in schizophrenia.** The main features of schizophrenia are positive symptoms (delusions and hallucinations; symptoms associated with loss of connection to reality), negative symptoms (impaired motivation, decreased spontaneous speech and social withdrawal) and cognitive impairment (Joyce Roiser, 2007). Cognitive impairments include deficits in attention, learning, memory, executive functions, working memory, and processing speed, suggesting that cortical dysfunctions are widespread (Heinrichs Zakzanis, 1998; Joyce et al., 2005; Wilk et al., 2005). However, schizophrenia is characterised by a high degree of heterogeneity in cognitive function. Nuechterlein et al. (2004) identified key cognitive domains that are impaired by changes in various neurological substrates and that can be altered differently by different pharmacological treatments (Nuechterlein et al. 2004). These domains include processing speed, attention/vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, social cognition (Nuechterlein et al., 2008).

**Cognitive dysfunctions in bipolar disorder.** Most meta-analyses have shown that bipolar patients are most affected in the areas of attention, verbal learning and memory, and executive functions, while premorbid intelligence remains normal (Bourne et al., 2013; Kurtz Gerraty, 2009). Although cognitive impairment occurs across the whole spectrum of the disease, it is often more pronounced during acute episodes (Bourne et al., 2013; Kurtz Gerraty, 2009). Bipolar disorder is highly hereditary, and often unaffected first-degree relatives and children of patients also have mild cognitive impairment (de la Serna et al., 2016). The cognitive impairments in bipolar disorder lead to high levels of impulsivity, poor decision-making and potentially dangerous risk-taking behaviour, which are common components of the course of the various stages of bipolar disorder, and are considered to be core features of the illness (Ramírez-Martín et al., 2020).

**Cognitive deficits in neurodegeneration diseases.** Memory loss is one of the earliest signs of Alzheimer's disease, and the diagnosis and monitoring of the disease depends on the assessment of episodic memory, such as free

and cued recall and autobiographical memory (Arvanitakis et al., 2019). Other diagnostic cognitive tests based on semantic memory, such as category recognition tasks (e.g., Category Fluency Test; Keefe et al., 2004), verbal fluency tasks (e.g., Verbal Fluency Test (VFT; Lezak et al., 2004)), and picture naming tasks, have also been shown to show poorer performance with Alzheimer's disease (Westfall and Lee, 2021). Patients also have lower attentional resources and spatial orientation abilities compared to healthy older adults (Albert et al., 2011; Arvanitakis et al., 2019).

Mild cognitive impairment (MCI) is a clinical condition that lies between Alzheimer's disease and normal cognitive decline with age, and can provide important insights into the slow progression of functional impairment before the diagnosis of Alzheimer's disease (Petersen, 2016). However, patients with MCI typically have sufficient cognitive resources to compensate for the functional decline, making the diagnosis of MCI challenging (Ranchet et al., 2017). Nevertheless, poorer performance on speech and language, spatial orientation, and reaction time tasks can be observed in MCI (Costa et al., 2020; Darby et al., 2002; Mueller et al., 2018). In addition, tests of episodic memory, perception (naming, orientation and object selection) and working memory can accurately predict 88 % of people who will develop memory impairment over the next 4.5 years (Belleville et al., 2014).

Multiple sclerosis is known to be caused by demyelination of the central nervous system and the loss of axons, which disrupts many connections between different areas of the brain and the information transmission (Smith et al., 1999). More than half of multiple sclerosis patients have cognitive impairment, which varies and results in different neuropsychological profiles during clinical assessment (Chiaravalloti and DeLuca, 2008). However, the most commonly affected cognitive domains are attention, processing speed and memory (Paul et al., 1998).

**Cognitive deficits in autism spectrum disorders.** Autism spectrum disorders (ASD) manifests itself in many different ways: a person with ASD may have a "classic" ASD accompanied by intellectual impairment, or it may be Asperger's Syndrome, where verbal abilities are outstanding (Moseley and Pulvermüller, 2018). Children with ASDs often have sensory processing difficulties leading to executive and cognitive impairments such as inhibitory control, auditory attention span, working memory, short-term verbal memory, concept formation and processing speed (Pastor-Cerezuela et al., 2020; Powell et al., 2017). Individuals with ASD also have impairments in action-related cognition, such as imitation and gesturing (Moseley and Pulvermüller, 2018). Cognition in adults with ASD is differentially affected by ageing, for example, studies of short-term and delayed recall, visual and spatial abilities,

information processing speed and cognitive flexibility have found age-related differences between adults with ASD and adults with typical development (Powell et al., 2017).

**Cognitive deficits in dyslexia.** Dyslexia is associated with persistent difficulties in the development of phonological abilities – characterised by slow and inaccurate word recognition (Hulme and Snowling, 2016). Children with dyslexia are characterised by difficulties with visual attention span, verbal working memory and processing speed, as well as impairments in executive control processes (Yuzaidey et al., 2018). Problems in reading and writing continue into adulthood and appear to be exacerbated when performance is assessed by speed (Reis et al., 2020).

# 3. METHODS

First, a systematic literature review was carried out to summarise the available scientific evidence on the relationship between gamma-band ASSRs and cognitive functions in studies of healthy subjects and patients with neuropsychiatric or developmental disorders.

Two experimental studies were then carried out. The first study, was carried out on a homogeneous sample of subjects (healthy, young males) in order to pinpoint the possible associations between 40 Hz ASSRs and different cognitive abilities. The second study aimed to investigate the relationship between cognitive abilities and EFR at 40 Hz and IGF.

# 3.1 Systematic literature review on the relationship between cognitive performance and gamma-range ASSR

The systematic review was carried out in collaboration with Dr Inga Griškova-Bulanova and Dr Jovana Bjekić. The thesis author contributed to all phases of the study: methodology, data search, data collection and analysis, drafting and editing of the description. The systematic review was performed in accordance with the Primary Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al., 2011; Page et al., 2021).

3.1.1 Literature search for a systematic review

The literature was gathered via searches in the PubMed, Web of Science, and Scopus databases. The search was conducted between June 2020 and January 2021, and the keywords included "auditory amplitude-modulated response", "auditory steady-state response", "auditory entrainment", "cognitive task", "behavioural task", "psychological task", "verbal task", "attention", "cognition" and "memory". First, the abstracts of the articles in the search results were reviewed. Where the abstract did not contain sufficient information, the methodological part of the article was revised. If several studies are included in an article, each of them is considered separately. In order to find other potentially relevant studies, the reference lists of the included articles were further manually checked. Figure 3.1 shows the process of searching and selecting studies of the systematic review.

#### 3.1.2 Selection of studies for systematic review

The following inclusion criteria were applied to each study found in the search: (1) study participants adults (aged 18 years or more); (2) EEG/MEG techniques with gamma-range (30-80 Hz) auditory stimulation were used; (3) at least one cognitive ability was assessed; (4) a statistical association was reported between the ASSR measurements and the cognitive abilities; (5) the article reported the original research. As this is the first systematic review of the association between gamma-range ASSRs and cognitive performance, in order to maximise the number of studies reviewed, studies involving not only healthy subjects, but also patients with neuropsychiatric and developmental disorders (e.g., schizophrenia, Alzheimer's disease, dyslexia, etc.) were included.

The following papers were excluded: (1) animal studies; (2) studies measuring ASSRs at frequencies other than gamma-range (up to 30 Hz or more than 80 Hz); (3) studies that did not use recognised cognitive assessment methods; (4) studies in which ASSRs were recorded during altered states (e.g., during high-cognitive-demand tasks, sleep, anaesthesia, or hallucinations); (5) studies in which ASSRs could be affected by brain-stimulation techniques (e.g., transcranial alternating current stimulation (tACS), transcranial magnetic stimulation (TMS)); (6) the description of the studies is not published in English. The titles and abstracts of all study descriptions, as well as the full content of some articles, were screened against the following selection criteria.



Figure 3.1 Flowchart of the study search and selection process.

### 3.1.3 Data extraction of studies included in the review

The following data was collected for each study: (1) sample (type, size, age, and gender composition); (2) neurocognitive assessment method (i.e., tasks used to assess cognitive performance); (3) auditory stimulation settings (frequencies, type, number of repetitions, and duration); (4) method of ASSR measurement (EEG/MEG, indices assessed, localisation, time interval); (5) correlation between ASSR measure(s) and neurocognitive measure(s).

To systematize the results, we grouped the neurocognitive performance assessment tasks that were used in the included studies into higher-order cognitive domains: (1) global cognition or intellectual ability (g), (2) attentional control and executive functions, (3) processing speed, (4) shortterm and working memory, (5) cognitive flexibility and reasoning, and (6) language abilities. It is important to note that this list is by no means a recognised classification of assessment of cognitive abilities, but merely an attempt to organise the tools used in studies.

### 3.1.4 Assessing the quality of the studies in the review

Typically, systematic reviews assess the quality of included studies (Higgins et al. 2019). This has also been done in this review. The potential bias is usually identified to ascertain the robustness of the data obtained (Furuya-Kanamori et al. 2021; Sterne et al. 2019; Higgins et al. 2019). Bias can occur at any stage of a study, whether in the planning, execution or analysis of the results; it can arise from the actions of the investigators, or it can be unavoidable due to the practical constraints of implementing research (Sterne et al., 2019; Higgins et al., 2019). It is usually not possible to determine the extent to which bias has affected the results of a particular study, so it is usually suggested to consider whether there is a risk of bias, rather than to state unequivocally whether the result is biased (Sterne et al., 2019; Higgins et al., 2019).

In accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019) guidelines and The Revised Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) (Sterne et al., 2019), the quality of the included articles was evaluated by two persons, the author of the thesis and the author's supervisor Dr Inga Griškova-Bulanova. In case of controversy, the opinion of Dr Jovana Bjekić, another co-author of the systematic review, was sought. The quality assessment focused on the main aspects of the study, assessing their reproducibility and replicability (National Academies of Sciences, Engineering, and Medicine, 2019): method of selection of subjects (selection bias), methods of measurement used (performance bias), measures validity and reliability (detection bias), acknowledgement of cognitive variables, methods of data processing (attrition bias), statistical power, comprehensiveness of the study description (paradigm description).

**1. Selection bias** is defined as the non-random distribution of factors that may influence the final indicators in the group of subjects (Padmanabhan,

2014). Selection bias may arise from the selective inclusion of participants based on their prognostic factors (e.g., severity of disease or presence of comorbidities), and hence from non-random selection of subjects. Also, inappropriate methods for selecting subjects are systematic methods, sometimes referred to as semi-randomisation (Higgins et al., 2019), where, for example, selection is based on the day of admission to hospital, which is not completely randomised. To avoid bias, subjects are selected using either completely random or probability sampling. Thus, it is important to consider the appropriateness of the selection of clinical cases and controls when assessing the reported results: whether the criteria for diagnosing clinical cases and the definitions used to describe conditions are appropriate, whether the same exclusion criteria are applied to all subjects, whether no attempt is made to include subjects who are more likely to be affected the effect in question, etc.

2. Performance bias – bias resulting from deviations from the intended design of a study or from the occurrence of unintended effects during the course of a study (Viswanathan et al., 2017). To avoid this bias, the interventions (e.g., stimuli) and conditions applied to subjects in studies are usually standardised (e.g., by creating a study protocol that is followed by all investigators) to ensure that all participants receive the same interventions and conditions. If, however, unforeseen additional effects on subjects arise during the course of the study that may affect the results, these can be monitored, evaluated and described (Viswanathan et al., 2017). Unfortunately, study reports may not indicate (1) the circumstances that led to the deviation from the original protocol, or (2) additional factors that arose during the course of the study that may have influenced the results (Higgins et al., 2019). In EEG studies, there may be performance risks if, for example, some subjects are allowed to rest in the middle of the study while others are not, as this relaxation can affect brain activity. Thus, when reviewing a study, it is important to consider whether the researchers followed the protocol and excluded the effects of any unintended factors that could bias the results. If there are biases unrelated to the study protocol, review authors should consider whether appropriate statistical methods were used to correct for their effects (Higgins et al., 2019).

**3.** Attrition bias occurs when data have not been properly handled (not using appropriate data processing or statistical methods) considering missing data values (due to non-response, participant exclusion or withdrawal, etc.), or when the reasons for missing data are not properly assessed (e.g., they are not discussed) (Babic et al., 2019). For example, the risk of this bias can arise when a study excludes all of a subject's results when only a few values are

missing, as this approach may skew the results (Kang, 2013). On the other hand, measured results may differ systematically from omitted results, so it is important to discuss the reasons for data loss and whether these reasons are related to the study methodology, the subjects, and whether the loss of such data is likely to affect the results (Higgins et al., 2019). For example, if participants who are more likely to be depressed are less likely to return for follow-up, this means that the measured average depression score of the participants will be systematically different from the true depression score. In EEG studies, missing data in the EEG recordings are often based on interpolation methods, i.e., the value of the variable is approximated from known values (Murray et al., 2008).

4. Detection bias arises from the way impacts and outcomes are measured and evaluated (Viswanathan et al., 2013). The risk of such bias may arise if (1) the method of measuring the results is inappropriate, (2) the results are not measured in the same way in different study groups, (3) the outcome evaluator may be biased, and/or (4) there is pre-existing knowledge that may influence the evaluation of the results (Higgins et al., 2019). Theoretically, studies are at risk of bias if they use insufficiently validated measures (Viswanathan et al., 2013). Therefore, the use of standardised measures (e.g., the use of biomarkers validated in previous studies in EEG studies) increases the reliability and validity of the results (Hersen, 2003). Differences in measurement methods between groups can also lead to unexpected adverse effects. For example, if some subjects are given a drug that causes headaches, which requires more EEG tests than usual, these subjects may show more abnormalities in their EEGs than others, simply because of the higher number of tests (increased likelihood of detecting the abnormality).

**5. Statistical power** is the probability that a test of statistical significance will show a significant effect when it actually exists (Bezeau and Graves, 2001). Statistical power may be insufficient due to the small sample size and low number of tests (Boudewyn et al., 2018). Large samples have a smaller standard error than small samples (Baguley, 2004). Therefore, conclusions drawn from a study with a small sample of participants can be misleading when applied to the whole population (Clayson et al., 2019). In simulations of real EEG data, it has been shown that with a small difference of 2  $\mu$ V between conditions and 16 trials per participant, the probability of detecting a difference between conditions, i.e., the statistical power, gradually increases from 0.6 to 1 as the number of subjects increases from 12 to 32 (Boudewyn et al., 2018). According to a review by Thuné et al. (2016) (which covered 29 studies comparing schizophrenia patient groups with healthy controls), the number of participants in ASSR studies is highly asymmetrically distributed,

with an average sample size of approximately  $29.7 \pm 43.4$  and a median sample size of 18, thus it is more appropriate to use the median as a reference of these sample sizes when assessing the potential risk of statistical power bias in ASSR studies.

6. Paradigm description, evaluated in terms of a transparent, accurate and comprehensive description of the methods of selection, data collection, analysis and conclusions, and the context of the study, which enables study replication (obtaining similar results using fresh data) and reproduction (obtaining previous results using data provided by the authors of the study) (Hensel, 2021; Asendorpf et al, 2016). Reproducibility and reproducibility, which facilitate scientific self-correction, are at the heart of the scientific method and are based on a rigorous and transparent scientific workflow, as well as on the disclosure of the data underpinning the results of research (Curty et al., 2022; Zwaan et al., 2018). For example, in the description of ASSR studies, it is essential to include information about the subjects (clinical condition, gender, age, etc.), the stimuli (frequency, type of intervals, number of repetitions, etc.) and the measurement methods (method used, location, duration, etc.). In cognitive ability research, it is important to provide information on the tasks used to measure ability (Cauchoix et al., 2018). In these studies, information about the context of the study is also important, as context can influence behaviour and thus the results of EEG and cognitive tasks (Cauchoix et al., 2018). Inadequate description of a study can be caused by a variety of factors: inadequate record-keeping, technological limitations, possible bias, legal obstacles, etc. (Ganley et al., 2022).

**7. Cognitive variables acknowledgement,** i.e., their analysis and discussion in study reports, is of particular relevance to this systematic review, as it aims to assess the cognitive correlates of ASSR. Although the selected studies use methods for assessing the subjects' abilities, their statistical relationship with the ASSR measurements may not be reported. This may be due to selective reporting (Page and Higgins, 2016). For example, in some cases, the results measured and analysed during the study may be omitted or partially reported in the narrative depending on the nature (magnitude, statistical significance, etc.) of the results (Higgins et al., 2019). On the other hand, sometimes studies collect additional data that are not directly relevant to the purpose of the study and are therefore not analysed in detail, e.g., they are only used to apply eligibility criteria to subjects – to validate a certain condition or diagnosis (McElroy and Ladner, 2014; Higgins et al., 2019).

Each study description was scored on a scale from 0 to 7, depending on the amount and quality of information provided. The risk of bias element to be assessed is scored 1 if all information is provided, 0.5 if some information has been provided but some aspects have been left unexplained or unstated, and 0 if no information has been provided on the element in question. These scores were then added together. A study description with a total score of at least 5 was considered to have a low risk of bias. A summary of the risk elements assessed and their control questions is presented in Table 3.1.

|   | Risk of bias<br>elements            | Control questions  |
|---|-------------------------------------|--|
| 1 | Selection bias                      | Were cases and controls selected appropriately<br>(e.g., appropriate diagnostic criteria or definitions,<br>equal application of exclusion criteria to case and<br>controls, sampling not influenced by exposure<br>status)? |
| 2 | Performance bias                    | Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?  |
| 3 | Attrition bias                      | If attrition (overall or differential nonresponse, loss<br>to follow-up, exclusion or withdrawal of<br>participants) was a concern, were missing data<br>handled appropriately?  |
| 4 | Detection bias                      | Were variables assessed/defined using valid and<br>reliable measures implemented consistently across<br>all study participants?  |
| 5 | Statistical power                   | Was the sample size adequate? Were the stimuli were repeated a sufficient number of times?   |
| 6 | Paradigm<br>description             | Was the description of the paradigm used provided<br>in full (stimuli characteristics, number of stimulus<br>presentations, inter-stimulus interval, response type,<br>etc.) and can it be replicable?                       |
| 7 | Cognitive variables acknowledgement | Were correlations between cognitive evaluation and ASSR measures discussed, and possible reasons attributed?   |

**Table 3.1** Risk of bias elements and control questions.

# 3.2 A study on the relationship between cognitive performance and the 40 Hz ASSR

The study was carried out at the Institute of Biosciences, Vilnius University Life Sciences Center. Permission to conduct the study was granted by the Vilnius Regional Biomedical Research Ethics Committee (12-02-2013, No. 158200-13-579-174). All subjects gave written informed consent to participate in the study. The research was carried out in collaboration with coauthors Dr Inga Griškova-Bulanova, Dr Aleksandras Voicikas, Dr Evaldas Pipinis, Dr Vytautas Jurkuvėnas, Povilas Tarailis and Mindaugas Kraulaidis. The author of this thesis contributed to all phases of this study: data collection and analysis, administration, drafting and editing of the description and dissemination. The study consisted of two parts: (1) measurement of cognitive abilities involving the processing of complex and simple information and (2) measurement of EEG indices.

### 3.2.1 Participants in the 40 Hz ASSR study

Thirty healthy, non-smoking right-handed males (females and left-handed were excluded due to the possible impact of hormonal fluctuations and handedness (Griškova-Bulanova et al., 2014; Melynyte et al., 2018)) were included in the study. One participant's data was excluded from the data analysis due to the poor quality of the EEG recording; another participant's data was not included due to technical problems with the cognitive ability tasks. Twenty-eight individuals (mean age 25.8, SD 3.3) were included in the final sample.

All participants had normal hearing thresholds (< 25 dB hearing level at octave frequencies). Before the study, all subjects abstained from alcohol (24 hours), nicotine (1 hour) and caffeine (1 hour).

### 3.2.2 Cognitive assessment in the 40 Hz ASSR study

The Psychology Experiment Building Language-based task battery (PEBL; Mueller and Piper, 2014) presented in Lithuanian (PEBL-Lt; compiled by Jurkuvenas, 2015) was used for cognitive assessment. Tasks measuring both simple and complex information processing speed were selected (Jurkuvenas, 2016). Before the testing began, each participant was given a brief explanation of the procedure. A short practical trial preceded each task. The following cognitive tasks were used:

**1. Two-Choice Response Time Task** (Logan et al., 1981) in which participants had to indicate the direction of an arrow on a computer screen in front of the participants by pressing either the left or the right button on the keyboard. Task measures included reaction time (RT), the number of errors and response efficiency (as a mean RT divided by the proportion of correct

responses on the test). The task is designed to measure the response time and simple information processing speed.

**2. Lexical Decision Task** (Meyer and Schvaneveldt, 1971), in which participants are asked to indicate whether a given word is correct or contains an error. RT, the number of errors and response efficiency used to evaluate lexical memory and the speed of processing complex information.

**3. Semantic Categorization Task** (Rosch, 1975), in which the participants successively presented with words, and have to indicate whether the word belongs to a particular category, e.g., furniture, animal, utensils, etc. The RTs, correct answers and efficiency scores are used to assess semantic processing and complex information processing speed.

**4. Tower of London Task (ToL)** (Shallice, 1982) requires participants to move the coloured disks to reach the goal configuration in as few moves as possible. The ToL mean task time, mean steps required to complete the task and mean move time (RT) are used to assess executive function, planning speed, problem-solving speed, and complex information processing speed.

**5.** The Stroop Task (Stroop, 1935), where you have to respond to the colour of the letters of a word on a computer screen rather than the meaning of the word. The task contains congruent (meaning of the word given, which specifies the colour name and the colour is congruent), incongruent (meaning of the word given, which specifies the colour name and the colour is incongruent), and neutral (the word does not specify the colour name) conditions. The task covers RT, error rate and response efficiency. The results are used to assess executive functions, attention, response inhibition and complex information processing speed.

### 3.2.3 Auditory stimulation in the 40 Hz ASSR study

The auditory stimuli (Fig. 3.2) were generated in MATLAB 2014 (The MathWorks, Inc., Natick, MA, USA). Subjects received auditory stimulus delivered binaurally through Sennheiser HD 280 PRO headphones (sound pressure level 60 dB, measured by DVM 401 dB metre, Velleman, TX USA). The 40 Hz clicks (bursts of white noise) lasted 500 ms and consisted of 20 identical clicks. Each trial was presented 150 times with 700-1000 ms interstimulus intervals. Participants were instructed to concentrate on the stimulus and to try to keep their gaze on the fixation cross shown on the computer screen in front of them.



**Figure 3.2** A schematic representation of the auditory stimulus used in the 40 Hz ASSR study – 40 Hz click train.

### 3.2.4 EEG recording in the 40 Hz ASSR study

ANT device (ANT Neuro, Hengelo, the Netherlands) with 64 Ag/AgCl WaveGuard Cap (International 10-20 System) was used to record the EEG. The impedance was kept below 20 k $\Omega$ , and the sampling rate was 1024 Hz. Mastoids (M1 and M2 electrodes) were used as reference points, and the ground electrode was positioned close to Fz. Simultaneously, electrooculograms (EOG) were recorded from above and below the left eye (vertical electrooculogram, VEOG) and the right and left outer canthi (horizontal electrooculogram, HEOG).

### 3.2.5 EEG processing in the 40 Hz ASSR study

EEGLAB for MatLab 2014 was used to perform offline EEG pre-processing (Delorme and Makeig, 2004). Multi-tapering and Thomas F-statistics were used to eliminate power-line noise, as implemented in the CleanLine plugin for EEGLAB (NITRC CleanLine: Tool). The data was visually inspected to detect noisy channels throughout the recording and then manually removed. An independent component analysis (ICA) was performed using EEGLAB's

ICA implementation ("runica" with default parameters); independent components related to eye movements were removed.

Further analysis of the data was performed using custom-written scripts based on EEGLAB (Delorme and Makeig, 2004) and Fieldtrip functions (Oostenveld et al., 2011). Epochs were created from -500 ms (before the stimulus) to 700 ms (after the stimulus). Data were baseline-corrected to the mean of the pre-stimulus period, and epochs were further visually inspected for the remaining artefacts. A time-frequency transformation was performed using a complex Morlet wavelet from the MATLAB Wavelet Toolbox; frequencies ranging from 1 to 120 Hz and in 1 Hz steps were used.

The phase-locking index (PLI), which indicates phase consistency across trials, and the event-related spectral perturbation (ERSP), which indicates changes in power due to event compared to a pre-stimulus baseline, were computed using the following formulas (Mørup et al., 2007):

$$PLI(c, f, t) = \frac{1}{N} \sum_{n}^{N} \frac{X(c, f, t, n)}{|X(c, f, t, n)|}$$
(3.1);

$$ERSP(c, f, t) = \frac{1}{N} \sum_{n=1}^{N} |X(c, f, t, n)|^{2}$$
(3.2);

for each channel c, frequency f and time point t are computed by taking the time-frequency decomposition X of each trial n. The data were baseline-adjusted by comparing to the mean pre-stimulus period. The estimates were divided by the mean prestimulus activity in the time window from -200 ms to 0 ms (absolute baseline correction).

The mean PLIs and ERSPs were calculated separately for left (F3, F1, FC1, C1, FC3, C3), central (Fz, FCz, Cz), and right (F4, F2, FC2, C2, FC4, C4) areas (Fig. 3.3) by averaging the data across 200-500 ms time and frequency of 35-45 Hz window.



**Figure 3.3** Electrode placement during the study. For PLI and ERSP analysis 15 electrodes were used, and separated into left (F3, F1, FC1, C1, FC3, C3) (light grey), central (Fz, FCz, Cz) (dark grey), and right (F4, F2, FC2, C2, FC4, C4) (grey) areas. GND - ground electrode. Figure adapted from Chi Qin et al. (2020).

3.2.6 Statistical analysis in the 40 Hz ASSR study

SPSSv20 was used for statistical analysis (SPSS Inc., Chicago, Illinois, USA). For each variable, descriptive statistics (means and standard deviations) were computed. Pearson's correlation coefficients were used to examine the relationship between cognitive measures and PLI/ERSP measurements.

The PLI and ERSP values were compared across areas (left vs centre vs right) using one-way analysis of variance (ANOVA) and subsequent post hoc analyses. No multiple-test correction was used due to the exploratory nature of the study. P-values less than 0.05 were considered significant.

3.3 A study of the relationship between IGFs and cognitive abilities

The study was carried out at the Institute of Biosciences, Vilnius University Life Sciences Center. Permission to conduct the study was granted by the Vilnius Regional Biomedical Research Ethics Committee (31-03-2020, No. 2020/3-1213-701). All subjects gave written informed consent to participate in the study. The research was conducted together with co-authors Dr Inga Griškova-Bulanova, Dr Aleksandras Voicikas, Dr Evaldas Pipinis, Dr Jovana Bjekić, Dr Vytautas Jurkuvėnas and Mindaugas Potapovas. The author of this thesis contributed to the conceptualization, data analysis and description of the study. The study consisted of two parts: (1) measurement of cognitive abilities involving the processing of complex and simple information and (2) EEG assessment.

### 3.3.1 Participants in the IGFs study

Thirty-seven healthy right-handed individuals (17 females) participated in the study (mean age 23.8, SD 4.7). All participants had normal hearing thresholds (< 25 dB hearing level at octave frequencies). Before the study, all subjects abstained from alcohol (24 hours), nicotine (1 hour) and caffeine (1 hour).

### 3.3.2 Cognitive assessment in the IGFs study

As in the previous study (see section 3.2), a battery of tasks in the Psychological Experimentation Building Language (PEBL; Mueller and Piper, 2014) was used to assess cognitive abilities, with the tests in Lithuanian (PEBL-Lt; Jurkuvenas, 2015). Tasks measuring both simple and complex information processing speed were selected (Jurkuvenas, 2016). Before the testing began, each participant was given a brief explanation of the procedure and a short practical test before each task. In this study, as in the first one, the Two-choice response time task (Logan et al., 1981), the Lexical Decision Task (Meyer and Schvaneveldt, 1971), the Semantic categorization task (Rosch, 1975), and the Tower of London Task (Shallice, 1982) were used (see section 3.2.2). In addition, the following cognitive tasks are included:

**1. Simple Reaction Time Task** (Seashore and Seashore, 1941), in which participants asked to detect the presence of a visual stimulus (X letter) as quickly as possible and press the button whenever stimulus occurred; used to measure RT. Allows to determine the simple information processing speed.

**2.** Arithmetic Decision Task (Perez, 1987) where subjects are presented with simple arithmetic expressions (simple addition or subtraction) and asked to indicate whether the outcome is correct or incorrect. In this task, RT is used to measure complex arithmetic information processing

**3.** Object Judgment Task (Mueller, 2010; Attneave and Arnoult, 1956; Collin and McMullen, 2002), in which the participant had to decide whether the two abstract waveforms presented are identical or different. The resulting RT measures the mental rotation speed and complex information processing speed.

### 3.3.3 Auditory stimulation in the IGFs study

As in the first study, the auditory stimuli (Fig. 3.4) were generated in MATLAB 2014 (The MathWorks, Inc., Natick, MA, USA). Subjects received auditory stimulus delivered binaurally through Sennheiser HD 280 PRO headphones (sound pressure level 60 dB, measured by DVM 401 dB metre, Velleman, TX USA).

The auditory stimulus consisted of 22 clicks that formed a click-based chirp: the intervals between the clicks were varied to cover the frequency range 35-55 Hz in 1 Hz steps. Thus, the inter-click time was adjusted to match the frequency, e.g., for 40 Hz stimulation, the inter-click period was 25 ms, for 50 Hz it was 20 ms. Each chirp stimulation train lasted 475.4 ms. In total of 300 trains of chirps were given, interspersed with single clicks, and interstimulus intervals were chosen randomly, in the range 700-1000 ms. Subjects were instructed to focus on the stimulation by mentally counting randomly presented single clicks interspersed between periodic noises, and at the end of each stimulation run report the count.



**Figure 3.4** A schematic representation of stimuli used in the study – a chirp stimulus spanning 35-55 Hz in 1 Hz step.

### 3.3.4 EEG recording and processing in the IGFs study

The EEG was recorded using the same equipment and methodology and the data were processed in a similar way to the previous study (see sections 3.2.4 and 3.2.5). Data processing differs only in a few aspects. Epochs were created from -500 ms (before the stimulus) to 1100 ms (after the stimulus onset). Data were baseline-corrected to the mean of the pre-stimulus period, and epochs were further visually inspected for the remaining artefacts.

The extracted PLIs and ERSPs were evaluated in the frequency range from 35-55 Hz in the frontocentral (Fz, Cz, FCz, C1, C2, F1, F2, FC1, FC2) region (Fig. 3.5). The data were baseline-adjusted by comparing to the mean pre-stimulus period: the mean prestimulus activity in the time window from -400 ms to 0 ms was subtracted from the response (relative baseline correction). The average response to each stimulation frequency (35-55 Hz in 1 Hz steps) was determined by utilising a time window of 100 ms from the stimulation line, consistently with the observed response windows in the time-frequency plots. PLI/ERSP data of the envelope following response at 40 Hz and IGFs were retrieved.



**Figure 3.5** Electrode placement during the study. For ERSP and PLI analysis 9 electrodes were used: Fz, Cz, FCz, C1, C2, F1, F2, FC1, FC2 (grey). GND - ground electrode. Figure adapted from Chi Qin et al. (2020).

3.3.5 Statistical analysis in the IGFs study

SPSSv20 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. For each variable, descriptive statistics (means and standard deviations) were computed. Pearson's correlation coefficients were used to examine the association between cognitive measures and PLI/ERSP measurements.

The PLI and ERSP results were compared at both frequencies, 40 Hz and IGF, using the paired sample t-test. The criterion for statistical significance was Bonferroni corrected to account for multiple comparisons, and p-values less than 0.004 (0.05/13) were considered significant. A summary of the characteristics of the two studies is given in Table 3.2.

|                               | ASSR study          | IGFs study         |
|-------------------------------|---------------------|--------------------|
| Subjects:                     |                     |                    |
| Number (males/females)        | 28 (28/0)           | 37 (20/17)         |
| Age (years)                   | 25.8±3.3            | 23.8±4.7           |
| Cognitive assessment:         |                     |                    |
| Simple reaction time task     | -                   | +                  |
| Two-choice response time task | +                   | +                  |
| Lexical decision task         | +                   | +                  |
| Arithmetic decision task      | -                   | +                  |
| Semantic categorization task  | +                   | +                  |
| Object judgment task          | -                   | +                  |
| Tower of London task          | +                   | +                  |
| Stroop task                   | +                   | -                  |
| Stimuli:                      |                     |                    |
| Туре                          | 40 Hz clicks        | 35-55 Hz click-    |
|                               |                     | based chirps       |
| Trials                        | 150                 | 300                |
| EEG assessment:               |                     |                    |
| Electrodes                    | left (F3, F1, FC1,  | frontocentral (Fz, |
|                               | C1, FC3, C3),       | Cz, FCz, C1, C2,   |
|                               | central (Fz, FCz,   | F1, F2, FC1, FC2)  |
|                               | Cz), and right (F4, |                    |
|                               | F2, FC2, C2, FC4,   |                    |
|                               | C4)                 |                    |
| Measures                      | ERSP/PLI at 40 Hz   | ERSP/PLI at 40 Hz  |
|                               |                     | and IGF            |
| Time window                   | 200-500 ms          | +100 ms from the   |
|                               |                     | stimulation line   |
| Frequency window              | 35-45 Hz            | 35-55 Hz in 1 Hz   |
|                               |                     | step               |

**Table 3.2** Summary of both study characteristics. ASSR study – a study of the relationship between cognitive abilities and 40 Hz ASSR, IGFs – a study of the relationship between IGFs and cognitive abilities.

ERSP — event-related spectral perturbation; PLI — phase-locking index; IGF — individual gamma frequency.

# 4. RESULTS

# 4.1 Results of a systematic review

The literature search yielded 1595 articles. After excluding duplicates and articles that did not meet the inclusion criteria, the systematic review included 21 studies (one study from each of the 21 articles) (Table 4.1). In eleven of the included studies, assessing the relationship between ASSR and cognitive correlates was one of the main aims of the study, while in the remaining ten studies cognitive correlates of the ASSR were presented as a secondary topic.

**Table 4.1.** Characteristics of studies investigating the associations between gamma-range ASSR and cognitive abilities (n.a. — not available; n.s. — not significant).

|   | Article                | Sample: size,<br>males / females,<br>mean age / age<br>range (SD)   | Neuropsychological Tasks   | Stimuli:<br>frequency,<br>type,<br>duration,<br>number | ASSR<br>measures<br>and site   | Correlations between ASSR and cognitive performances  |
|---|------------------------|---|--|--|--|---|
| 1 | Arrondo et al.<br>2009 | Healthy controls:<br>22; n.a. (similar)<br>Patients with<br>multiple<br>sclerosis:<br>27; 10/17; 44.11<br>(11.45) | <ul> <li>Brief Repeatable Battery–<br/>Neuropsychological (BRB-N; Rao, 1990):</li> <li>(1) Bushke Selective Reminding Test (SRT),</li> <li>(2) 10/36 Spatial Recall Test (SPART),</li> <li>(3) Oral version of the Symbol Digit Modalities Test (SDMT),</li> <li>(4) Paced Auditory Serial Addition Task with a 3 s Interval (PASAT-3),</li> <li>(5) Semantic Word List Generation (WLG).</li> </ul> | 1-120 Hz;<br>chirp;<br>1.61 s;<br>500<br>sweeps        | EEG;<br>Frequency<br>and amplitude<br>of the<br>maximal<br>response;<br>at Fz and Cz | Healthy controls: n.s.<br>Patients with multiple sclerosis:<br>SDMT and the frequency of the<br>maximal amplitude-following<br>responses around 40 Hz<br>( $r = 0.524$ , $p = 0.010$ );<br>PASAT-3 and the frequency of the<br>maximal amplitude-following<br>responses around<br>40 Hz ( $r = 0.483$ , $p = 0.012$ );<br>WLG and the frequency of the<br>maximal amplitude-following<br>responses around 40 Hz<br>( $r = 0.437$ , $p = 0.023$ ). |

| 2 | Bartolomeo et<br>al. 2019 | Healthy controls:<br>19; 14/5;<br>22.9 (3.6)<br>Early phase of<br>psychosis:<br>34; 24/7;<br>22.0 (4.3)          | The Brief Assessment of Cognition in<br>Schizophrenia (BACS; Keefe et al.,<br>2008).   | 40 Hz;<br>clicks;<br>500 ms;<br>8 trials         | EEG;<br>Power;<br>at Fz   | Healthy controls: n.s.<br>Early phase of psychosis: n.s.   |
|---|---------------------------|--|--|--|---|--|
| 3 | Gaskins et al.<br>2019    | Healthy younger<br>subjects:<br>15; n.a.;<br>22.3 (2.7)<br>Healthy older<br>subjects:<br>15; n.a.;<br>70.3 (3.8) | Wechsler Adult Intelligence Scale–<br>Third Edition, (WAIS-III; Wechsler,<br>1997; original version by Wechsler,<br>1955):<br>(1) Digit Symbol Coding,<br>(2) Symbol Search. | 40, 80 Hz;<br>AM tone;<br>300 ms;<br>1024 sweeps | EEG;<br>SNR;<br>at Cz   | Healthy younger subjects:<br>n.s. for 80 Hz ASSR; n.a. for<br>40 Hz ASSR.<br>Healthy older subjects:<br>n.s. for 80 Hz ASSR; n.a. for<br>40 Hz ASSR. |
| 4 | Hirano et al.<br>2020     | Healthy controls:<br>24; 20/4;<br>44.1 (7.3)<br>Chronic stage<br>schizophrenia:<br>23; 19/4;<br>45.6 (9.1)       | Information Subscale of the Wechsler<br>Adult Intelligence Scale–Fourth<br>Edition (WAIS-IV; Wechsler, 2008;<br>original version by Wechsler, 1955).                         | 20, 30,<br>40 Hz;<br>clicks;<br>500 ms           | EEG;<br>PLI,<br>evoked<br>power,<br>induced<br>power;<br>tangential and<br>radial dipoles<br>in each<br>hemisphere<br>above primary<br>auditory<br>cortex | Healthy control: n.s.<br>Chronic stage schizophrenia: n.s.   |

| 5 | Hirtum et al. | Healthy controls:  | Literacy, included:  | 40 Hz;                            | EEG;   | Healthy controls: n.s.  |
|---|---------------|--|--|-----------------------------------|--|---|
|   | 2019          | 18; 8/10;<br>18-25 years<br>Dyslexia:<br>20; 10/10;<br>18-25 years | <ol> <li>(1) Standardized Word–Reading Test</li> <li>(Ol. Een–Minuut–Test, EMT; Brus and<br/>Voeten, 1979),</li> <li>(2) Pseudo–Word Reading Test (ol. De<br/>Klepel: Een Test Voor Leesvaardigheid<br/>Van Pseudo–Woorden, Klepel; Van<br/>Den Bos et al., 1994),</li> <li>(3) a Spelling Test (Ol. Algemene<br/>Toets Gevorderde Spelling Van Het<br/>Nederlands, AT-GSN; Ghesquière,<br/>1998).</li> <li>Spoonerisms Task (Poelmans et al.,<br/>2011).</li> </ol> | AM tone;<br>300 ms;<br>300 epochs | SNR;<br>temporal-<br>parietal and<br>occipital<br>regions: left<br>(TP7, P1, P3,<br>P5, P7, P9,<br>PO3, PO7,<br>O1) and right<br>(TP8, P2, P4,<br>P6, P8, P10,<br>PO4, PO8,<br>O2) | Dyslexia:<br>Literacy and 40 Hz neural<br>background activity in the right<br>hemisphere (r = -0.35, p = 0.033);<br>Spoonerisms task and 40 Hz neural<br>background activity in the right<br>hemisphere (r = -0.39, p = 0.017);<br>RAN and 40 Hz neural background<br>activity in the right hemisphere<br>(r = -0.39, p = 0.017). |
|   |               |  | <ul> <li>Random Automatized Naming (RAN)</li> <li>Included:</li> <li>(1) Objects and (2) Colours</li> <li>(Boets et al. 2007),</li> <li>(3) Digits (De Vos et al. 2017) and (4)</li> <li>Letters (Vanvooren et al. 2017).</li> </ul>   |                                   |  |   |

| 6 | Kim et al.<br>2019      | Healthy controls:<br>30; 13/17;<br>43.33 (12.95)<br>Schizophrenia:<br>33; 16/17;<br>42.21 (10.99) | Trail Making Test–A and B version in<br>Korean (TMT-A and TMT-B; Korean<br>version by Seo et al., 2006; original<br>version by Reitan, 1955).<br>Verbal Fluency Test (VFT; Lezak et<br>al., 2004).<br>Korean–Auditory verbal Learning Test   | 40 Hz;<br>clicks;<br>500 ms;<br>150 trials     | EEG;<br>Mean evoked<br>power, ITC;<br>at Cz  | Healthy controls: n.s.<br>Schizophrenia:<br>Verbal fluency mean evoked power<br>at 40 Hz (r = 0.223, p = 0.019). |
|---|-------------------------|---|--|--|--|--|
|   |                         |   | (K-AVLT; From Rey–Kim Memory<br>Test, RKMT (Korean version by Kim,<br>1999, original version by Rey, 1941)).   |  |  |  |
| 7 | Kirihara et al.<br>2012 | Healthy controls:<br>188; 94/94;<br>43.9 (11.1)<br>Schizophrenia:<br>234; 182/52;<br>44.5 (8.8)   | The Wide Range Achievement Test 3<br>(WRAT3; Wilkinson, 1993; original<br>version by Jastak and Bijou 1946)<br>Reading Subtest.<br>California Verbal Learning Test<br>(CVLT-2; Delis, 2000; original version<br>by Delis, 1987) List A Trials 1-5.<br>Wisconsin Card Sorting Test–64 Card<br>version (WCST-64; Heaton, 1993;<br>Original version by Berg, 1948).<br>Letter–Number Sequencing Test (LNS;<br>Gold et al., 1997). | 30, 40 Hz;<br>clicks;<br>500 ms;<br>200 trials | EEG;<br>Amplitude,<br>PLI, cross<br>frequency<br>coupling,<br>modulation<br>index;<br>at FCz | Healthy controls: n.s.<br>Schizophrenia: n.s.  |

| 8 | Koshiyama et | Healthy control:  | Wechsler Adult Intelligence Scale-   | 40 Hz;                           | EEG;                                | Healthy control: n.s.   |
|---|--------------|---|--|----------------------------------|-------------------------------------|---|
|   | al. 2020a    | 283; n.a.<br>Schizophrenia:<br>428; n.a.  | Third Edition, (WAIS-III; Wechsler,<br>1997; original version by Wechsler,<br>1955) Letter–Number Sequencing<br>(LNS).               | clicks;<br>500 ms;<br>200 trials | ERSP;<br>at Fz                      | Schizophrenia:<br>40 Hz ASSR predicted LNS scores<br>(standardized coefficient $\beta = 0.15$ ,<br>$p < 8.3 \times 10^{-3}$ ).  |
|   |              |   | California verbal Learning Test<br>(CVLT-2; Delis, 2000; original version<br>by Delis, 1987) List A Trials 1-5.                      |                                  |                                     | I   |
|   |              |   | Wisconsin Card Sorting Test (WCST;<br>Berg, 1948).   |                                  |                                     |   |
| 9 | Koshiyama et | Healthy control:  | Wechsler Adult Intelligence Scale-   | 40 Hz;                           | EEG;                                | Healthy control: n.a.   |
|   | al. 2020b    | 293; 141/152;<br>44.7 (11.4)  | Third Edition (WAIS-III; Wechsler, 1997; original version by Wechsler,   | clicks;<br>500 ms;               | PLI,<br>8 dipoles                   | Schizophrenia:  |
|   |              | Schizophrenia:<br>427; 309/118;<br>45.5 (9.5)   | <ul><li>1955):</li><li>(1) Letter–Number Sequencing (LNS),</li><li>(2) Letter–Number Span (LN Span).</li></ul>                       | 200 trials                       | above primary<br>auditory<br>cortex | ASSR in the right temporal cortex $(r = 0.16, p = 0.01);$<br>LNS scores with PLI of 40 Hz in  |
|   |              |   | California verbal Learning Test Second<br>Edition (CVLT-2; Delhi, 2000; original<br>version by Delhi, 1987) List A Trials<br>1-5.    |                                  |                                     | the right temporal cortex (r = 0.13, $p = 0.046$ ) and left temporal cortex (r = 0.17, $p = 0.02$ );<br>WRAT3 scores with PLI of 40 Hz  |
|   |              | Reading Subtest of t<br>Achievement Test-3<br>Wilkinson, 1993; or<br>Jastak and Bijou, 19 | Reading Subtest of the Wide Range<br>Achievement Test–3 (WRAT-3;<br>Wilkinson, 1993; original version by<br>Jastak and Bijou, 1946). |                                  |                                     | in the left temporal cortex ( $r = 0.17$ , $p = 0.01$ );<br>CVLT-2 scores with PLI of 40 Hz<br>in the left temporal cortex ( $r = 0.14$ , $p = 0.04$ ) and left superior frontal<br>cortex ( $r = 0.17$ , $p = 0.02$ ). |

| 10 | Koshiyama et | Healthy control: | Wechsler Adult Intelligence Scale-     | 40 Hz;     | EEG;    | Combined sample:                |
|----|--------------|------------------|--|------------|---------|---------------------------------|
|    | al. 2021a    | 503; 234/269;    | Third Edition (WAIS-III; Wechsler,     | clicks;    | PLI and | 40 Hz PLI and ERSP with LN Span |
|    |              | 43.7 (12.8)      | 1997; original version by Wechsler,    | 500 ms;    | ERSP;   | (p < 0.00042)                   |
|    |              | Schizophrenia    | 1955):                                 | 200 trials | at Fz   |                                 |
|    |              | 695. 177/218.    | (1) Letter–Number Sequencing (LNS),    |            |         |                                 |
|    |              | 45.5 (10.2)      | (2) Letter–Number Span (LN Span).      |            |         |                                 |
|    |              |                  | California verbal Learning Test Second |            |         |                                 |
|    |              |                  | Edition (CVLT-2; Delhi, 2000; original |            |         |                                 |
|    |              |                  | version by Delhi, 1987) List A Trials  |            |         |                                 |
|    |              |                  | 1-5.                                   |            |         |                                 |
|    | Lehongre et<br>al. 2011 | Healthy controls:<br>21; 11/10;<br>24.38 (3.85)<br>Dyslexic:<br>23; 14/9;<br>24.61 (4.57) | Reading Fluency Assessed by Alouette<br>Test (pranc. Test De l'Alouette 2ème<br>Édition; Lefavrais, 1967; original<br>version by Lefavrais, 1965).<br>Random Automatized Naming (RAN;<br>from the Phonological Assessment<br>Battery (Frederickson et al., 1997)).<br>Composite Measure of Phonology<br>(PHONO) Included:<br>(1) the Wechsler Adult Intelligence<br>Scale (WAIS-III), Digit Span,<br>(2) Spoonerism Task (Soroli et al.,<br>2010),<br>(3) Pseudo–Words Test (Dupoux et al.,<br>2001; original version by Dupoux et<br>al., 1997). | 10-80 Hz;<br>chirp;<br>5.4 s;<br>80 sweeps | MEG;<br>Power,<br>power<br>asymmetry<br>(left-right);<br>at planum<br>temporale<br>(PT),<br>superior<br>temporal<br>sulcus (STS) | Healthy controls:<br>Reading speed and 30 Hz ASSR<br>power ( $p < 0.05$ ), left and right PT;<br>Composite measure of phonology<br>and 30 Hz ASSR power ( $p < 0.05$ )<br>in left PT.<br>Dyslexic:<br>Spoonerism task and 30 Hz power<br>asymmetry (left minus right)<br>( $r = -0.450$ , $p = 0.047$ ) (effect was<br>mostly driven by nonword<br>repetition ( $r = 0.44$ , $p = 0.04$ ));<br>RAN and 30 Hz power asymmetry<br>( $r = 0.552$ , $p = 0.006$ );<br>Digit span and 45-65 Hz magnitude<br>in left PT (at 58 Hz: $r = -0.542$ ,<br>p = 0.009), left PFC ( $r = -0.486$ ,<br>p = 0.022) and left STS ( $r = -0.511$ ,<br>p = 0.015). |
|----|-------------------------|---|---|--|--|---|
| 12 | Leonhardt et al. 2020   | Schizophrenia or<br>schizoaffective<br>disorder:<br>17; 14/3;<br>21.5 (3.8)               | The Brief Assessment of Cognition in<br>Schizophrenia (BACS; Keefe et al.,<br>2008).  | 40 Hz<br>clicks;<br>500 ms;<br>80 trials   | EEG;<br>Power;<br>at Fz and Cz   | Schizophrenia or schizoaffective disorder: n.s.   |

| 13 | Light et al.<br>2006  | Healthy controls:<br>80; n.a.;<br>33.6 (9.95)<br>Schizophrenia:<br>100; n.a.;<br>42.5 (8.31)               | The Wide Range Achievement Test 3<br>(WRAT3; Wilkinson, 1993; original<br>version by Jastak and Bijou 1946)<br>Reading Subtest.<br>California verbal Learning Test<br>(CVLT-2; Delis, 2000; original version<br>by Delis, 1987) List A 1-5.<br>Wisconsin Card Sorting Test–64 Card<br>version (WCST-64; Heaton, 1993;<br>original version by Berg, 1948); | 30, 40 Hz;<br>clicks;<br>500 ms;<br>200 trials                                | EEG;<br>Evoked power<br>and PLI;<br>at FCz   | Healthy controls: n.s.<br>Schizophrenia:<br>LNS and power at 40 Hz ( $r = 0.32$ , $p < 0.01$ ). |
|----|-----------------------|--|---|---|--|---|
|    |                       |  | Letter–Number Sequencing Test (LNS; Gold et al., 1997).   |   |  |   |
| 14 | Murphy et al.<br>2020 | Healthy controls:<br>17; 9/8;<br>28.87 (5.98)<br>Early-stage<br>schizophrenia:<br>12; 12/0;<br>27.5 (6.89) | The Brief Assessment of Cognition in<br>Schizophrenia (BACS; Keefe et al.,<br>2008) Composite Score.  | 20, 30,<br>40 Hz;<br>clicks;<br>1000 ms;<br>100 trials<br>each of<br>10 block | MEG;<br>Amplitude<br>and phase-<br>amplitude<br>coupling;<br>at combined<br>region of<br>bilateral | Healthy controls: n.s.<br>Early-stage schizophrenia: n.s.<br>Chronic stage schizophrenia: n.s.  |
|    |                       | Chronic stage<br>schizophrenia:<br>16; 13/3;<br>33.63 (6.94)   |   |   | transverse<br>temporal<br>cortex and<br>superior<br>temporal<br>gyrus                              |   |

| 15 | Puvvada et al.<br>2018 | Healthy controls:<br>108; 71/37;<br>37.9 (13.8)<br>Schizophrenia:<br>128; 86/42;<br>37.8 (13.1)<br>First-degree<br>relatives of<br>schizophrenia<br>patients:<br>55; 17/38;<br>46.6 (13.6) | Wechsler Adult Intelligence Scale–<br>Third Edition (WAIS-III; Wechsler,<br>1997; original version by Wechsler,<br>1955) Digit Span.   | 40, 80 Hz;<br>clicks;<br>375 ms and<br>187.5 ms;<br>75 trials, each<br>containing<br>15 clicks; | EEG;<br>Power and<br>PLI;<br>at frontal-<br>central<br>electrodes | Healthy controls: n.s.<br>Schizophrenia:<br>Digit span and power at 40 Hz<br>( $r = 0.20$ , $p = 0.033$ ).<br>First-degree relatives of<br>schizophrenia patients:<br>Digit span and power at 40 Hz<br>( $r = 0.42$ , $p = 0.003$ ). |
|----|------------------------|--|--|---|---|--|
| 16 | Rass et al.<br>2010    | Healthy controls:<br>87; 40/47;<br>41.0 (10.3)<br>Euthymic bipolar<br>disorder:<br>22; 43.6 (10.5)<br>Acute bipolar<br>disorder:<br>43; 42.6 (10.3)  | Wechsler Adult Intelligence Scale–<br>Third Edition (WAIS-III; Wechsler,<br>1997; original version by Wechsler,<br>1955):<br>(1) Picture Completion,<br>(2) Digit Symbol Coding,<br>(3) Digit Span,<br>(4) Similarities. | 30, 40,<br>50 Hz;<br>clicks;<br>467-480 ms;<br>80 trials  | EEG;<br>MTP and PLI;<br>at FCz                                    | Healthy controls: n.s.<br>Bipolar disorder: n.s.   |

| 17 | Rass et al.<br>2012 | Healthy controls:<br>56; 26/30;<br>38.75 (10.4) | Wechsler Adult Intelligence Scale–<br>Third Edition (WAIS-III; Wechsler,<br>1997; original version by Wechsler, | 30, 40,<br>50 Hz;<br>clicks; | EEG;<br>MTP and PLI;<br>at FCz | Healthy controls:<br>Similarities and 40 Hz PLI $(r = 0.38, p < 0.01);$   |
|----|---------------------|---|---|------------------------------|--------------------------------|---|
|    |                     | Schizophrenia / schizoaffective                 | 1955):<br>(1) Picture Completion,   | 467-480 ms;<br>80 trials     |                                | Symbol Coding and 50 Hz MTP $(r = 0.26, p = 0.03)$ .  |
|    |                     | disorder:<br>42; 23/19;<br>36.86 (12.8)         | <ul><li>(2) Digit Symbol Coding,</li><li>(3) Digit Span,</li><li>(4) Similarities.</li></ul>                    |                              |                                | Schizophrenia and schizoaffective disorder: Similarities and 40 Hz MTP ( $r = 0.34$ , $p = 0.04$ ), 40 Hz                                       |
|    |                     | First-degree<br>relatives of<br>schizophrenia   |   |                              |                                | PLI ( $r = 0.34$ , $p = 0.04$ );<br>Digit span and 50 Hz PLI<br>( $r = 0.38$ , $p = 0.02$ ).  |
|    |                     | patients:<br>35; 13/22;<br>36.03 (12.5)         |   |                              |                                | First-degree relatives of<br>schizophrenia patients:<br>Similarities and 40 Hz PLI  |
|    |                     | Schizotypal<br>personality<br>disorder:         |   |                              |                                | (r = 0.39, p = 0.03);<br>Similarities and 50 Hz PLI<br>(r = 0.45, p = 0.01).  |
|    |                     | 34; 20/14;<br>37.35 (9.2)                       |   |                              |                                | Schizotypal personality disorder:<br>Similarities and 40 Hz MTP<br>(r = 0.34, p = 0.04);<br>Similarities and 50 Hz PLI<br>(r = 0.40, p = 0.02). |

| 18 | Rojas et al. | Healthy controls:   | Wechsler Abbreviated Scale of  | 32, 40,                                     | MEG;  | Healthy controls: n.s.             |
|----|--------------|---|--|---|---|------------------------------------|
| 10 | 2011         | 20; 7/13;<br>43.84 (6.86)<br>Parents of<br>children with<br>ASD:<br>21: 6/15: | <ul> <li>Wechsler Abbreviated Searc of</li> <li>Intelligence Second Edition (WASI-II;</li> <li>Wechsler, 1999, original version by</li> <li>Wechsler, 1981):</li> <li>(1) Verbal IQ,</li> <li>(2) Performance IQ,</li> <li>(3) Full Scale IQ.</li> </ul> | 48 Hz;<br>AM tone;<br>500 ms;<br>150 trials | PLI,<br>evoked,<br>induced and<br>total power | Parents of children with ASD: n.s. |
|    |              | 43.67 (7.33)  |  |   |   |                                    |
|    |              |   |  |   |   |                                    |

| 19 | Sun et al. | Healthy controls:        | MATRICS Consensus Cognitive               | 40 Hz;     | EEG;           | Healthy controls:                   |
|----|------------|--------------------------|---|------------|----------------|-------------------------------------|
|    | 2018       | 30; 16/14;               | Battery (MCCB; Chinese version by         | clicks;    | Power, PLI,    | Mazes test and PLI (r =0.66);       |
|    |            | 34.2 (10.3)              | Yu and Yao, 2014; original version by     | 500 ms;    | ITPC;          | Mazes test and ITPC ( $r = 0.69$ ); |
|    |            | Schizophrania            | Nuechterlein et al, 2008): (1) Trail      | 150 trains | 128 electrodes | Trail Making Test: Part A and PLI   |
|    |            | $24 \cdot 13/11 \cdot$   | Making Test a (TMT-A; Reitan, 1955),      |            |                | (r = 0.56, p < 0.05);               |
|    |            | 24, 15/11,<br>33.0(11.0) | (2) Brief Assessment of Cognition in      |            |                | Trail Making Test: Part A and       |
|    |            | 55.0 (11.0)              | Schizophrenia (BACS; Keefe                |            |                | ERSP ( $r = 0.62, p < 0.05$ );      |
|    |            |                          | et al., 2008) Symbol Coding Test,         |            |                | Cognitive assessment total score    |
|    |            |                          | (3) Hopkins verbal Memory Test-           |            |                | and PLI (r = 0.48, p < 0.05);       |
|    |            |                          | Revised (HVLT-R, Brandt and               |            |                | Cognitive assessment total score    |
|    |            |                          | Benedict, 2001),                          |            |                | and ERSP ( $r = 0.59, p < 0.05$ )   |
|    |            |                          | (4) Wechsler Adult Intelligence Scale–    |            |                | Schizophrenia:                      |
|    |            |                          | Third Edition (WAIS-III; Wechsler,        |            |                | Mazes test and 40 Hz PLI            |
|    |            |                          | 1997)Spatial Span Test,                   |            |                | (r = 0.55, p < 0.05):               |
|    |            |                          | (6) WAIS-III Letter–Number Span           |            |                | Mazes test and ITPC ( $r = 0.54$ ,  |
|    |            |                          | (LNS),                                    |            |                | p < 0.05)                           |
|    |            |                          | (6) Neuropsychological Assessment         |            |                |                                     |
|    |            |                          | Battery (NAB; Stern and White, 2003)      |            |                |                                     |
|    |            |                          | Mazes,                                    |            |                |                                     |
|    |            |                          | (7) Category Fluency Test: Animal         |            |                |                                     |
|    |            |                          | Naming Test (Nuechterlein et Al,          |            |                |                                     |
|    |            |                          | 2008),<br>(8) Continuous Derformente Test |            |                |                                     |
|    |            |                          | (8) Continuous Performance Test-          |            |                |                                     |
|    |            |                          | at al. 1088)                              |            |                |                                     |
|    |            |                          | (0) the Drief Vieween stiel Menser        |            |                |                                     |
|    |            |                          | (9) the Driel visuospatial Memory         |            |                |                                     |
|    |            |                          | 1 est-Reviseu (D vivii-R, Defiedict et    |            |                |                                     |
|    |            |                          | AI, 1996, Original version by Brandt,     |            |                |                                     |
|    |            |                          | 1771).                                    |            |                |                                     |

| 20 | Tada et al.<br>2016        | Healthy controls:<br>21; 11/10;<br>22.4 (3.3)<br>First-episode<br>schizophrenia:<br>13; 8/5;<br>24.5 (5, 0) | BACS-J: verbal Memory, Digit<br>Sequencing Task (Digit Span), Token<br>Motor Task, Category Fluency, Letter<br>Fluency, Symbol Coding, Tower of<br>London. | 50, 40 HZ;<br>clicks;<br>500 ms;<br>200 trials | 50, 40 Hz, 1<br>clicks; 1<br>500 ms; 1<br>200 trials 1 | 30, 40 Hz,       1         clicks;       1         500 ms;       1         200 trials       1   | 30, 40 Hz;       1         clicks;       1         500 ms;       1         200 trials       1 | 30, 40 Hz;<br>clicks;<br>500 ms;<br>200 trials | Iz; EEG;<br>PLI and<br>ERSP; late<br>ls latency;<br>at FCz | Healthy controls: n.a.<br>First-episode schizophrenia:<br>Symbol coding and the 40 Hz PLI<br>( $r = 0.75$ , $p = 0.003$ ) and ERSP<br>( $r = 0.76$ , $p = 0.003$ ).<br>Ultra-high-risk individuals: n.s. |  |
|----|----------------------------|---|--|--|--|---|---|--|--|--|--|--|--|--|--|--|
|    |                            | 24.3 (3.9)<br>Ultra-high-risk<br>individuals:<br>15; 9/6;<br>22.1 (4.0)                                     |  |  |  |   |   |  |  |  |  |  |  |  |  |  |
| 21 | van Deursen<br>et al. 2011 | Healthy controls:<br>20; 12/8;<br>69.5 (6.1)  | The Cognitive Subscale of the<br>Alzheimer's Disease Assessment Scale<br>(ADAS-Cog; Mohs et al., 1983).  | 40 Hz; clicks;<br>450 ms;<br>80 trials         | EEG;<br>Power;<br>at T5, T6, O2,                       | Combined sample:<br>ADAS-cog and 40 Hz power at T5<br>(r = 0.43, p = 0.019) and T6 $(r = 0.38,$ |   |  |  |  |  |  |  |  |  |  |
|    |                            | Mild<br>Alzheimer's<br>disease:<br>15; 11/4;<br>75.2 (6.9)  |  |  | Fz, Pz, Cz   | p = 0.028).   |   |  |  |  |  |  |  |  |  |  |
|    |                            | Mild cognitive<br>impairment:<br>20; 12/8;<br>70.6 (7.2)  |  |  |  |   |   |  |  |  |  |  |  |  |  |  |

ERSP — event-related spectral perturbation, ITPC — inter-trial phase coherence, MTP — mean trial power, PLI — phase-locking index, SNR — signal-to-noise ratio; n.a. — not available; n.s. — not significant. It should be noted that the missing statistics were not provided in the articles themselves.

The majority of studies evaluated cognitive performance on tasks within a visual modality. In addition, very specific EEG measures were associated with very general measures of cognitive abilities. The following methods were used to assess cognitive skills in some studies: BACS (Bartolomeo et al., 2019; Leonhardt et al., 2020; Murphy et al., 2020; Tada et al., 2016)<sup>\*</sup>, Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II) (Rojas et al., 2011), ADAS-cog (van Deursen et al., 2011), MCCB (Sun et al., 2018). Three of the studies evaluated only global cognitive functioning (Bartolomeo et al., 2019; Hirano et al., 2020; Leonhardt et al., 2020). In contrast, some studies targeted specific functions, e.g., short-term and working memory applying Digit span (Puvvada et al., 2018) or Phonological awareness measured by Spoonerism task (Van Hirtum et al., 2019).

The majority of included studies evaluated the EEG/MEG response to repeated click stimulation in the gamma frequency range; however, differences in stimulation duration, stimulus characteristics, and interstimulus interval settings, as well as acquisition methods, were found. Most of the studies used click stimuli. Several studies used amplitude-modulated sounds (Gaskins et al., 2019; Rojas et al., 2011; Van Hirtum et al., 2019) or chirp-based stimulation (Arrondo et al., 2009; Lehongre et al., 2011). The main ASSR outcome measures were power and phase synchronization/consistency; two studies provided signal-to-noise ratio evaluations (Gaskins et al., 2019; Van Hirtum et al., 2019) and one study — IGF evaluations (Arrondo et al., 2009).

Most studies focused on the evaluation of the response during whole stimulation duration. However, Rass et al. (2010; 2012), Sun et al. (2018), and Gaskins et al. (2019) did not include the early response (0-100 ms). Murphy et al. (2020) and Tada et al. (2016) evaluated only the late-latency gamma (starting at 200 ms after stimulus onset) activity. Arrondo et al. (2009) and Lehongre et al. (2011) focused on the time-window of the maximal gamma response occurrence.

Three of the studies utilized MEG recordings (Lehongre et al., 2011; Murphy et al., 2020; Rojas et al., 2011). EEG recordings were made using a reference electrode on the nose and/or as a reference point the average of all electrodes (Kim et al., 2019; Koshiyama et al., 2020a; Molina et al., 2020; Puvvada et al., 2018; Sun et al., 2018a; Tada et al., 2016). The EEG results

<sup>\*</sup> Here and in the text below, the authors of the studies included in the systematic review that used these tasks are cited; the authors of the tasks themselves are listed in Table 4.1.

are reported mostly for fronto-central locations with the exception of van Deursen et al. (2011) and Van Hirtum et al. (2019), who analysed temporal locations. All the cognitive tasks used in the studies reviewed, grouped according to the cognitive domains, are presented in Table 3.2.

**Table 4.2** The cognitive tasks used in the studies included in the systematic review were grouped according to cognitive domains (see Table 4.1 for the studies using the tasks and the authors of the tasks).

|   | Domain             | Assessment  |
|---|--------------------|---|
| 1 | Global cognition   | MATRICS Consensus Cognitive Battery (MCCB),         |
|   | or intellectual    | Wechsler Abbreviated Scale of Intelligence – Second |
|   | ability (g)        | edition (WASI-II), Alzheimer's Disease Assessment   |
|   |                    | Scale (ADAS-cog), Brief Assessment of Cognition in  |
|   |                    | Schizophrenia (BACS).                               |
| 2 | Attentional        | Continuous Performance Test-Identical Pairs,        |
|   | control and        | (CPT-IP), Paced Auditory Serial Addition Test,      |
|   | executive          | PASAT-3, Category fluency, Semantic word list       |
|   | functions          | generation (WLG).                                   |
| 3 | Processing speed   | Symbol search, Trial making test (TMT), Digit-      |
|   |                    | Symbol Coding, Symbol Digit Modalities Test         |
|   |                    | (SDMT), Verbal fluency test (VFT), Picture          |
|   |                    | Completion, Letter fluency.                         |
| 4 | Short-term and     | Digit span, Spatial span, Letter-Number span,       |
|   | working memory     | Letter-number sequencing, The Brief Visuospatial    |
|   |                    | Memory Test-Revised (BVMT-R), Verbal memory,        |
|   |                    | Hopkins Verbal Learning Test, Buschke Selective     |
|   |                    | Reminding Test (SRT), 10/36 Spatial recall test,    |
|   |                    | California Verbal Learning Test (CVLT)              |
| 5 | Cognitive          | Wisconsin Card Sorting Test (WCST) Similarities,    |
|   | flexibility and    | Mazes, Tower of London (ToL).                       |
|   | reasoning          |   |
| 6 | Language abilities | Verbal IQ, Reading, Pseudo-words test, Auditory     |
|   |                    | verbal learning, Spoonerisms task, Literacy, Random |
|   |                    | Automatized Naming, WRAT-3 Reading subtest,         |
|   |                    | Information subscale.                               |

## 4.1.1 Quality of the studies in the review

The results of the quality assessment are shown in Table 4.3. The majority of included studies had a low risk of bias, with the exception of Bartolomeo et al. (2019) and Gaskins et al. (2019), which under-reported data.

**Table 4.3.** Bias risk assessment scores. A score of 0 indicates a high risk of bias, a score of 0.5 indicates a medium risk of bias and a score of 1 indicates a low risk of bias. The descriptions of the assessed criteria (1-7) are given in Table 3.1. Studies with a higher overall risk of bias (total score less than 5 points) are shown in grey.

|                         | <b>Risk of bias elements</b> |     |   |     |     |   |     |       |  |
|-------------------------|------------------------------|-----|---|-----|-----|---|-----|-------|--|
| Article                 | 1                            | 2   | 3 | 4   | 5   | 6 | 7   | TOTAL |  |
| Arrondo et al. 2009     | 1                            | 1   | 1 | 1   | 1   | 1 | 1   | 7     |  |
| Bartolomeo et al. 2019  | 1                            | 1   | 1 | 1   | 0.5 | 0 | 0   | 4.5   |  |
| Gaskins et al. 2019     | 0                            | 0.5 | 1 | 0.5 | 0.5 | 0 | 1   | 3.5   |  |
| Hirano et al. 2020      | 1                            | 1   | 1 | 1   | 1   | 1 | 0   | 6     |  |
| Hirtum et al. 2019      | 0.5                          | 1   | 1 | 1   | 1   | 1 | 1   | 6.5   |  |
| Kim et al. 2019         | 1                            | 1   | 1 | 1   | 1   | 1 | 1   | 7     |  |
| Kirihara et al. 2012    | 1                            | 1   | 1 | 1   | 1   | 1 | 1   | 7     |  |
| Koshiyama et al. 2020a  | 1                            | 1   | 1 | 1   | 1   | 1 | 1   | 7     |  |
| Koshiyama et al. 2020b  | 1                            | 1   | 1 | 1   | 1   | 1 | 1   | 7     |  |
| Koshiyama et al. 2021a  | 1                            | 1   | 1 | 1   | 1   | 1 | 1   | 7     |  |
| Lehongre et al. 2011    | 0.5                          | 0.5 | 1 | 1   | 1   | 1 | 1   | 6     |  |
| Leonhardt et al. 2019   | 1                            | 1   | 1 | 1   | 0.5 | 1 | 1   | 6.5   |  |
| Light et al. 2006       | 0.5                          | 1   | 1 | 1   | 1   | 1 | 1   | 6.5   |  |
| Murphy et al. 2020      | 1                            | 1   | 1 | 1   | 1   | 1 | 0.5 | 6.5   |  |
| Puvvada et al. 2018     | 1                            | 1   | 1 | 1   | 1   | 1 | 1   | 7     |  |
| Rass et al. 2010        | 1                            | 1   | 1 | 1   | 1   | 1 | 0.5 | 6.5   |  |
| Rass et al. 2012        | 1                            | 1   | 1 | 1   | 1   | 1 | 0   | 6     |  |
| Rojas et al. 2011       | 1                            | 0   | 1 | 1   | 1   | 1 | 1   | 6     |  |
| Sun et al. 2018         | 1                            | 1   | 0 | 1   | 1   | 1 | 1   | 6     |  |
| Tada et al. 2016        | 1                            | 1   | 1 | 0.5 | 0.5 | 1 | 1   | 6     |  |
| van Deursen et al. 2011 | 1                            | 1   | 1 | 1   | 0.5 | 1 | 1   | 6.5   |  |

# 4.1.2 Correlations between ASSR and cognitive abilities found in studies reviewed

Correlations of gamma-band ASSR were most often found with speed of performance on tasks assessing information processing speed, short-term and/or working memory. For example, the Symbol coding task was used in six studies (Arrondo et al., 2009; Gaskins et al., 2019; Rass et al., 2012, 2010; Sun et al., 2018; Tada et al., 2016). Of these, three studies found a correlation: in two of them, task performance was positively associated with ASSR in patients with schizophrenia (Tada et al., 2016), as well as in patients with multiple sclerosis (Arrondo et al., 2009) and in healthy control subjects (Rass et al., 2012). Similarly, the Digit Span test was employed in seven studies (Kim et al., 2019; Lehongre et al., 2011; Puvvada et al., 2018; Rass et al., 2012, 2010; Sun et al., 2018; Tada et al., 2016). Four of them showed a correlation of the results with ASSR: a positive correlation in two studies with schizophrenia patients (Puvvada et al., 2018; Rass et al., 2012) and with firstdegree relatives of schizophrenic patients (Puvvada et al., 2018), as well as a negative correlation in one study with dyslexic individuals (Lehongre et al., 2011). Letter-number sequencing task was employed in five reports (Kirihara et al., 2012; Koshiyama et al., 2020a; Light et al., 2006; Molina et al., 2020; Tada et al., 2016), four showing a positive association between task performance in patients with schizophrenia and 40 Hz ASSR measures (Koshiyama et al., 2020a; Light et al., 2006; Molina et al., 2020; Tada et al., 2016).

In healthy participants, the gamma-range ASSR was related to cognitive flexibility and reasoning as measured by complex tasks such as Similarities (WAIS-III) (Rass et al., 2010) and Mazes Test (MCCB) (Sun et al., 2018). Additionally, ASSR was related to behavioural indicators of processing speed, i. e., performance on Trial making test (MCCB) (Sun et al., 2018) and Symbol coding (WAIS-III) (Rass et al., 2012).

Five out of sixteen studies assessing patients with psychotic symptomatology (schizophrenia, schizoaffective disorder, schizotypal personality disorder) showed no relationship between gamma-range ASSR and cognitive performance (Bartolomeo et al., 2019; Hirano et al., 2020; Kirihara et al., 2012; Leonhardt et al., 2020; Murphy et al., 2020). In studies of these patients where a correlation was found, higher ASSR has been associated with better performance on short-term memory tasks (such as Digit span and Letter number sequencing) (Koshiyama et al., 2020a; Light et al., 2006; Molina et al., 2020; Puvvada et al., 2018; Tada et al., 2016), as well as in the performance on tasks tapping speeded access to long term/semantic

memory (like Verbal fluency) (Kim et al., 2019) and on simple speeded tasks (like Symbol coding) (Tada et al., 2016). However, correlations between ASSR and complex reasoning tasks such as the Mazes Test (Sun et al., 2018), Similarities from the WAIS-III Battery (Rass et al., 2012) and the Tower of London (BACS) (Tada et al., 2016) are contradictory.

In other patient groups, gamma-range ASSRs were indicative of impairment in disease-relevant cognitive domains. Namely, studies that assessed language abilities in dyslexia reported a negative correlation with phonological awareness (i.e., performance on Spoonerism task) and phonological fluency (as measured by RAN), as well as literacy and nonword repetition (Lehongre et al., 2011; Van Hirtum et al., 2019). Also, a higher 40 Hz ASSR was related to better overall functioning assessed with the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog) in patients with a mild form of Alzheimer's disease (van Deursen et al., 2011). Multiple sclerosis patients who performed better on various cognitive tasks from the BRB-N showed a IGF at higher gamma frequencies (Arrondo et al., 2009). It should be noted that in a study of patients with bipolar disorder, no association was found between ASSR and performance on several WAIS-III tests assessing cognitive abilities (Rass et al., 2010).

# 4.2 Results of the study on the relationship between cognitive performance and 40 Hz ASSR

4.2.1 Cognitive performance in the 40 Hz ASSR study

The performance on cognitive tests corresponded to the previously reported outcomes (Jurkuvėnas, 2016; Scarpina et al., 2021). The means and standard deviations of the results obtained are shown in Table 4.4.

| Cognitive task        | Measure                | Mean (ms) | SD     |
|-----------------------|------------------------|-----------|--------|
| Two-choice response   | Mean RT                | 387.12    | 49.92  |
| time task             | Error                  | 0.57      | 0.84   |
|                       | Efficiency             | 392.6     | 48.55  |
| Stroop test           | Congruent mean RT      | 817.49    | 162.29 |
|                       | Congruent error        | 0.54      | 0.79   |
|                       | Congruent efficiency   | 836.88    | 166.22 |
|                       | Incongruent mean RT    | 985.26    | 213.47 |
|                       | Incongruent error      | 1.68      | 1.63   |
|                       | Incongruent efficiency | 1072.52   | 281.78 |
|                       | Neutral mean RT        | 878.65    | 196.68 |
|                       | Neutral error          | 0.68      | 0.90   |
|                       | Neutral efficiency     | 902.8     | 189.82 |
| Tower of London task  | Mean task time         | 15452.73  | 5238.5 |
|                       | Mean move time         | 2057.72   | 677.16 |
|                       | Mean moves             | 60.68     | 6.0    |
| Lexical decision task | Mean time              | 1395.61   | 306.72 |
|                       | Error                  | 2.79      | 1.83   |
|                       | Efficiency             | 1562.97   | 392.97 |
| Semantic              | Mean time              | 744.08    | 89.0   |
| categorisation task   | Error                  | 0.32      | 0.55   |
|                       | Efficiency             | 750.14    | 89.29  |

**Table 4.4** Means and standard deviations of cognitive measures (authors of the tasks are listed in section 3.2.2).

RT — response time

## 4.2.2 Auditory responses in the 40 Hz ASSR study

A typical ASSR to 40 Hz stimulation was observed with a frontal-central distribution corresponding to previous reports (Spencer et al., 2009; Yokota et al., 2017; Koshiyama et al., 2021b). The grand-averaged topographical plots of PLIs and ERSPs in response to 40 Hz stimulation across a time range of 0-500 ms in 100 ms intervals are presented in Figure 4.1.



**Figure 4.1** Topographical plots of the PLI (upper panel) and ERSP (lower panel) in response to 40 Hz stimulation within a 0-500 ms time window in 100 ms bins.

The maximal response was observed between 200-300 ms, in line with earlier observations (Light et al., 2006; Maharajh et al., 2007; Ross and Pantev, 2004; Saupe et al., 2009b). The time-course of PLI and ERSP values is plotted in Figure 4.2.



**Figure 4.2** The averaged time course of PLIs (upper panel) and ERSPs (bottom panel) in response to 40 Hz stimulation in the left, centre, and right areas. The line shows a linear correlation. Correlation estimates are given as r and p values.

Table 4.5 displays the means and standard deviations of PLIs and ERSPs for the left, right, and centre areas. Somewhat higher PLI and ERSP values were observed over the centre, but the differences were negligible.

**Table 4.5** The means and standard deviations of the PLI and ERSP values during 200-500 ms for the left, centre, and right areas in response to 40 Hz stimulation.

| Site | I    | .eft | Ce   | entre | R    | ight |
|------|------|------|------|-------|------|------|
|      | mean | SD   | mean | SD    | mean | SD   |
| PLI  | 0.26 | 0.13 | 0.32 | 0.12  | 0.26 | 0.11 |
| ERSP | 0.42 | 0.24 | 0.50 | 0.23  | 0.41 | 0.18 |

PLI — phase-locking index, ERSP — event-related spectral perturbation

4.2.3 Correlations between the 40 Hz ASSR and cognitive indices

The study found significant correlations were found between the mean number of steps on the Tower of London task and 40 Hz ASSR measures PLI/ERSP for the left (PLI: r = 0.55, p < 0.01; ERSP: r = 0.57, p = 0.01), central (PLI: r = 0.37, p = 0.05; ERSP: r = 0.42, p = 0.03) and right regions (PLI: r = 0.43, p = 0.02; ERSP: r = 0.46, p = 0.01). Figure 4.3 shows scatterplots of PLIs and ERSPs against mean number of moves in the Tower of London Task. No correlations were observed for RTs on other tasks.\*

<sup>\*</sup> All data from the study is available on the Open Science Framework database. Link: https://doi.org/10.17605/OSF.IO/UDES2



**Fig 4.3** Scatterplots of 40 Hz PLIs and ERSPs against mean moves in the Tower of London Task. Plots are presented separately for the left, central and right regions.

# 4.3 Results of a study of the relationship between IGFs and cognitive abilities

4.3.1 Cognitive performance in the IGFs study

The performance on cognitive tests corresponded to the previously reported outcomes (Jurkuvėnas, 2016; Körber et al., 2015; Perez, 1987). The means and standard deviations of the RTs obtained are shown in Table 4.6.

| Task                                  | Response times (ms) |        |  |  |
|---------------------------------------|---------------------|--------|--|--|
|                                       | Mean                | SD     |  |  |
| Simple reaction time task             | 294.38              | 50.75  |  |  |
| Two-choice response time task         | 378.16              | 61.19  |  |  |
| Arithmetic decision task              | 1116.12             | 327.84 |  |  |
| Lexical decision task                 | 1248.64             | 357.79 |  |  |
| Semantic categorization task          | 751.97              | 209.61 |  |  |
| Object judgement task                 | 814.68              | 188.15 |  |  |
| Tower of London task (mean move time) | 1997.52             | 626.12 |  |  |

**Table 4.6** Means and standard deviations of mean response times (RTs) on cognitive tasks (authors of the tasks are listed in sections 3.2.2 and 3.3.2).

## 4.3.2 Auditory responses in the IGFs study

Envelope following responses correspond to previous findings (Artieda et al., 2004; Griškova-Bulanova et al., 2021; Pipinis et al., 2018), showing an anterior-central topography and clear activation in the 35-55 Hz range. The grand averaged topographies of PLI and ERSP at 35, 40, 45, 50, 55 Hz and the time-frequency plots are depicted in Figure 4.4. The PLI and ERSP curves were extracted for each subject to estimate response maximums. These curves are plotted in Figure 4.5.



**Figure 4.4** PLI and ERSP time-frequency graphs. Solid white line indicates stimulus, white dashed line indicates a window of +100 ms from the stimulation line. The grand-averaged topographies for the envelope-following response at 35, 40, 45, 50, and 55 Hz stimulation are shown along with the time-frequency plots.



**Figure 4.5** Individual PLI and ERSP curves of each subject, and IGF violin plots (top corners).

The IGFs were identified at frequencies ranging from 36 to 53 Hz, with mean maximums at 41-42 Hz. The PLI and ERSP values were extracted at 40 Hz and at IGFs. The means and standard deviations for PLIs and ERSPs are summarized in Table 4.7.

|      |      | 40 Hz EFR | IGF-EFR | t-Test      | IGF   |
|------|------|-----------|---------|-------------|-------|
| PLI  | Mean | 7.07      | 7.63    | -6.534,     | 41.89 |
|      | SD   | 2.39      | 2.20    | _ p<0.001 _ | 2.27  |
| ERSP | Mean | 1.29      | 1.35    | -6.849,     | 42.19 |
|      | SD   | 0.20      | 0.20    | _ p<0.001 _ | 2.57  |

**Table 4.7** Means and standard deviations of PLIs and ERSPs at 40 Hz and IGFs.

PLI — phase-locking index; ERSP — event-related spectral perturbation; EFR — envelope following response; IGF — individual gamma frequency.

## 4.3.3 Correlations between IGFs and cognitive indices

To explore the relationship between EFRs and cognitive abilities, Pearson's correlation coefficients were calculated for all measures separately (Table 4.8). RTs from the ToL task statistically significantly correlated with ASSR measures: negative correlations were observed between RTs on ToL and PLIs and ERSPs for responses at both 40 Hz and IGFs. The correlations between task scores and ASSR scores in IGF were very similar to those at 40 Hz which is to be expected as both PLI and ERSP were highly correlated at both frequencies (r > 0.95). Scatterplots of PLIs and ERSPs at IGFs against mean move times in the Tower of London task are presented in Figure 4.6. No correlations were observed for RTs on other tasks.

PLI Task ERSP 40 Hz **IGF-EFR IGF** 40 Hz IGF-IGF EFR EFR EFR Simple reaction 0.05 0.04 -0.030.03 0.03 0.01 r time 0.79 0.83 0.86 0.86 0.85 0.94 р Two-choice 0.08 0.02 -0.180.09 0.03 -0.20r 0.87 response time 0.62 0.93 0.29 0.60 0.23 р Arithmetic -0.13-0.15-0.06-0.12-0.16-0.12r decision 0.46 0.36 0.47 0.34 0.49 0.71 р -0.10Lexical decision r -0.11-0.02-0.03-0.07-0.180.58 0.52 0.70 0.28 0.90 0.87 р Semantic -0.20-0.23-0.04-0.15-0.18-0.10r categorization 0.23 0.18 0.80 0.39 0.28 0.55 р Object judgment r -0.16-0.160.21 -0.10-0.120.10 task 0.35 0.34 0.21 0.54 0.47 0.57 р Tower of London r -0.50-0.550.08 -0.49 0.09 -0.510.002 < 0.001 0.65 0.002 0.001 0.60 р

**Table 4.8** Pearson correlation coefficients and p-values between ERF measures and RTs of cognitive tasks (authors of the tasks are listed in sections 3.2.2 and 3.3.2).



**Figure 4.6** Scatterplots of phase-locking indexes (PLIs) and event-related spectral perturbations (ERSPs) at individual gamma frequencies (IGFs) against the Tower of London task mean move times.

### 5. DISCUSSION

ASSR is a brain electrical response to periodic auditory stimuli (Galambos et al., 1981) and is emerging as a promising method for studying cognitive processes in healthy and clinical populations (Kirihara et al., 2012; Leonhardt et al., 2020; Light et al., 2006; Puvvada et al., 2018; Rass et al., 2012; Sun et al., 2018). 40 Hz ASSR is regulated by arousal and attentional states (Gander et al., 2010; Górska and Binder, 2019; Griškova et al., 2007; Griškova-Bulanova et al., 2011; Skosnik et al., 2007; Voicikas et al., 2016), and is associated with the degree of cognitive deterioration in neurodegenerative disorders (van Deursen et al., 2011). However, the relationship between gamma-range ASSR and cognitive processes has not yet been fully established and characterised (Santarelli et al., 1995; Manting et al., 2021 and others). One possible reason for this lack of data is that there have not yet been studies looking at both simple and complex information processing and their correlations with ASSR in a homogeneous sample of subjects, by age and sex. Moreover, it is common to use stimuli at 40 Hz in ASSR studies (Picton, 2013; Picton et al., 2003a), but stimulation in the gamma frequency range elicits the greatest response for each subject at the IGF (Artieda et al., 2004; Dolphin, 1997; Griškova-Bulanova et al., 2021; Purcell et al., 2004). Therefore, ASSRs at IGF may better reflect unique network characteristics than at 40 Hz frequency.

In these studies, we aimed to determine whether there is a relationship between cognitive abilities and gamma-range ASSR: we reviewed and systematically analysed the available data in the literature and performed an exploratory study of the association between 40 Hz and cognitive abilities in a homogeneous sample of young men. We also carried out another study to determine whether there is a relationship between cognitive function and ASSR arising at IGFs.

### 5.1 Systematic literature review

The literature review was conducted to collect, organise and critically appraise previous studies on the relationship between gamma-range ASSR and cognitive functions. The systematic review included twenty-one studies. While the auditory stimulation parameters for ASSR were fairly consistent, the test protocols for measuring cognitive abilities varied significantly. The vast majority of studies have been conducted to assess ASSR in clinical populations. First of all, it can be noted that although most of the studies reviewed in the systematic review used multiple tasks, they measure specific and often narrow cognitive domains. Except for Rojas et al. (2011), who used WASI-II, no study has carried out a comprehensive assessment of cognitive ability using a full battery of tests/tasks covering all aspects of cognitive ability as defined by well-established models such as the Cattell-Horn-Carroll theory of cognitive abilities (Carroll, 2003, 1993; Schneider and McGrew, 2012). Therefore, it is difficult to reliably assess the nature of the relationship between ASSR and cognitive functions on the basis of the currently available evidence. However, a comprehensive assessment of cognitive abilities has been carried out using clinical condition-specific test batteries (Sun et al, 2018; Murphy et al, 2020; Leonhardt et al., 2019; Bartolomeo et al., 2019). Thus, the quality of the scientific evidence for the association of cognition and ASSR with pathological rather than normal functioning is currently higher.

Correlations of gamma-band ASSR were most often found with speed of performance on tasks assessing information processing speed, short-term and/or working memory. These results might imply that individual differences in gamma-range ASSR reflect the individual differences in the ability to focus attention, maintain and manipulate the information in short term memory storage. It should be noted, however, that these correlations were most pronounced in patients with impaired short-term and/or working memory, such as schizophrenia patients (Kirihara et al., 2012; Koshiyama et al., 2020; Puvvada et al., 2018; Rass et al., 2012; Tada et al., 2016), multiple sclerosis patients (Arrondo et al., 2009), and subjects with dyslexia (Lehongre et al., 2011).

Studies of individuals with dyslexia have shown that gamma-range ASSR also correlate with the degree of language impairment (Lehongre et al., 2011; Van Hirtum et al., 2019). These results are in line with the relationships between ASSRs and performance on speech recognition tasks described in other studies (Alaerts et al., 2009; Dimitrijevic et al., 2004; Manju et al., 2014). Manju et al. (2014) suggested that the relationship between ASSR and the degree of speech impairment may be related to altered perception of the temporal modulation of speech (Manju et al., 2014). On the other hand, the correlation may also reflect the common core function such as attentional control and ability to maintain and manipulate content in the short-term memory storage. Namely, language comprehension and production strongly depend on the temporary storage and processing of information, i.e., working memory (Baddeley, 2003). This is especially prominent in different language disorders (e.g., see Archibald, 2017). This is confirmed by Lehongre et al. (2011) study, which found correlations of ASSRs in a group of dyslexic

individuals with both a short-term/working memory task (Digit Span) and language abilities tasks (Lehongre et al., 2011). Therefore, it is plausible that the observed relationship between gamma-range ASSRs and language performance does not reflect differences in linguistic abilities per se but rather stem from individual differences in more fundamental ability process information in short-term/working memory.

Additionally, performance on several tasks taping at cognitive flexibility and reasoning correlated to measures of gamma-range ASSRs in healthy controls and patients with schizophrenia (Rass et al., 2012; Sun et al., 2018). However, tasks evaluating cognitive flexibility and reasoning are defined by high versatility, and the functions they assess are intricately covering attentional control/executive functioning and memory processes (Deák and Wiseheart, 2015; Suchy, 2009). This makes it difficult to assess the observed relationship.

Only one of the studies analysed in the systematic review examined the relationship between ASSR IGFs and cognitive functions. This study by Arrondo et al. (2009) showed that IGF is negatively associated with attentional control and executive task performance in a group of patients with multiple sclerosis. Other studies not included in the review found that performance on a gap detection task in the auditory stimuli was also correlated with IGFs (Baltus Herrmann, 2015; Purcell et al., 2004). A correlation was also found between IGF and working memory assessed at different stages of sedation during anaesthesia (Andrade et al., 1996; Munglani et al., 1993). Taken together, these findings suggest that the state of the neural networks associated with IGF may also be related to temporal resolution perception and information processing speed and efficiency.

# 5.1.1 Generalization of the results of the review and guidelines for further research

The results of the systematic review suggest that gamma-range differences in ASSR reflect key aspects of cognitive functioning – attentional control and information processing in both healthy and clinical populations. However, this conclusion is not yet fully justified because (1) cognitive performance related to ASSR was not systematically assessed, (2) test protocols for measuring cognitive abilities varied considerably, (3) the vast majority of the studies were designed to assess ASSR in clinical populations, (4) none of the studies performed a comprehensive assessment of cognitive abilities using a battery of tests/tasks that covered all aspects of cognitive abilities, (5) some studies

had relatively small samples, (6) highly specific EEG parameters were often associated with very general cognitive indicators, (7) although the results of the cognitive flexibility and reasoning skills tasks correlate with the gammaband ASSR, it is difficult to interpret these results due to the universality of these tasks, and (8) the relationship between gamma-range ASSR and the degree of language impairment may also reflect changes in general information processing skills.

However, even with the same stimulation settings, ASSR and cognitive assessment approaches, different correlational outcomes were reported (e.g., see Kirihara et al., 2012; Koshiyama et al., 2021; Light et al., 2006; Rass et al., 2012, 2010). This suggests that interindividual subject characteristics, such as age or gender, might have a moderation-like effect as these are known to affect both cognitive performances (Halpern and LaMay, 2000; Verhaeghen, 2013) and ASSRs (Griškova-Bulanova et al., 2013; Kirihara et al., 2012; Melynyte et al., 2018). Outcomes may also have been influenced by differences in transient arousal state and/or attentional focus levels (Griškova-Bulanova et al., 2013; Wang et al., 2018), use of psychotropic substances (including psychotropic drugs) (Hong et al., 2004; Rass et al., 2010), psychopathology (Isomura et al., 2016; Spencer et al., 2009; Rass et al., 2010), the general level of global functioning and the stage of disease in neuropsychiatric patients (Ahmed et al., 2020; Zhou et al., 2018; Rass et al., 2010) could have affected the relationships. Also, the gamma-range ASSR measures could be potentially compromised by myogenic and micro-saccadic activity (Hipp and Siegel, 2013). Therefore, future studies should adopt the designs that enable exploring the magnitude of the moderating effects of these variables. For example, in studies of language abilities, it is also necessary to assess working or short-term memory in order to test whether the relationship of gamma-band ASSR to language abilities is only related to language abilities per se, and not to individual baseline information-processing skills. In addition, more research is needed on the relationship between cognitive skills and ASSR in different populations, this is particularly important when investigating various neuropsychiatric conditions (see, for example, Kim et al., 2019).

### 5.2 Discussion of the research results

In both conducted studies, associations were found between EEG measures of ASSRs and the Tower of London (ToL) task (from the PEBL-Lt Battery compiled by Jurkuvenas, 2016). ToL task assesses complex aspects of

executive function, planning, and problem-solving abilities (Kremen et al., 2009). In the study of the relationship between cognitive performance and 40 Hz ASSR, individuals who completed more steps in ToL had higher PLI and ERSP measures of 40 Hz ASSR. In a study of the relationship between IGFs and cognitive abilities, subjects with shorter movement times showed higher PLI and ERSP responses at both 40 Hz and IGF.

#### 5.2.1 Discussion of the 40 Hz ASSR study results

Unexpectedly, in the study of the relationship between 40 Hz ASSR and cognitive performance, individuals who performed more ToL (PEBL-Lt) movements, and therefore performed the task less efficiently, had stronger and more synchronised ASSR. Sun et al. (2018) found a positive correlation between the results of the Mazes test (from the MCCB; Yu and Yao, 2014 and Nuechterlein et al., 2008) and the 40-Hz ASSR phase-locking properties (Sun et al., 2018). Rass et al. (2012) study showed a positive correlation between 40 Hz ASSR phase synchrony and Similarity test results (Rass et al., 2012). Thus, in these studies, individuals with more synchronised ASSRs performed better on tasks designed to assess planning and problem-solving skills (Sun et al., 2018; Rass et al., 2012). Moreover, none of the three studies using the Wisconsin Card Screening Task (WCST) (Heaton, 1993; Berg, 1948) found any association with gamma-range ASSR in either schizophrenia patients or healthy subjects (Kirihara et al. 2012; Koshiyama et al. 2020a; Light et al. 2006). In addition, Tada et al. (2016), in whose study the ToL task included in the BACS was used (Kaneda et al. 2007; Keefe et al. 2004), also found no association with the 40 Hz ASSR in any of the three subject groups: (1) patients with first-episode schizophrenia, (2) individuals at high risk of developing schizophrenia, and (3) healthy individuals (Tada et al., 2016). Thus, the results of these studies are also different from those of our 40 Hz ASSR study. On the other hand, Díez et al. (2014a) found a negative correlation between ToL (from the BACS; Keefe et al. 2004) performance and total gamma power (35-45 Hz) during performance of the P300 Oddball task in schizophrenic patients and their family members, although no corresponding relationship was found among healthy controls (Díez et al. 2014a). ToL scores in the BACS (Keefe et al. 2004) are based on the number of correct moves, so a negative correlation with the total power in the gammarange implies that the less efficient performers of the task had a higher gamma-range response (Díez et al. 2014a). In addition, Díez et al. (2014b) obtained when assessing ToL and noise power in the gamma-range

(the amount of background oscillatory activity in the gamma range) (Díez et al., 2014b). Noise power in the frontal region of the brain has been shown to be negatively associated with the ToL and hence reasoning and problemsolving abilities of schizophrenic patients (Díez et al., 2014b). Díez et al. (2014a, 2014b) concluded that a higher gamma-band response may indicate excessive activation of neural networks, which interferes with efficient ToL performance. The results of these studies are consistent with our cognitive study, and therefore it is possible that participants with high ASSR, i.e., stronger responses to gamma-range stimuli, performed worse in ToL (PEBL-Lt) due to overactivation of neural networks.

### 5.2.2 Discussion of the results of IGFs study

The study on the relationship between IGFs and cognitive abilities used a different approach to investigate the response to the periodic stimulation. In order to determine the IGFs, the ASSRs elicited by the envelope of chirp oscillations, also known as the envelope-following response (EFR) (Dolphin, 1997), which covers the frequency range of 35-55 Hz, was analysed. The IGFs of the subjects ranged from 35 to 53 Hz, while the majority of subjects had IGFs around 40 to 42 Hz. However, in order to compare the results with the existing literature, PLI and ERSP were also calculated for the same group of subjects at 40 Hz. The indices obtained at the IGF correlated strongly with those obtained at 40 Hz, and the indices at both frequencies correlated with the same scores on cognitive ability tasks.

At both 40 Hz and IGF, ASSRs responses were negatively correlated with average move time on the ToL (PEBL-Lt) task. This suggests that individuals with higher gamma-frequency EFR synchrony perform faster on reasoning and problem-solving tasks. This finding is consistent with results by Sun et al. (2018), indicating a positive correlation between performance on complex planning and reasoning tasks such as the Mazes test from MCCB and results by Rass et al. (2012) showing a positive relationship between outcomes on Similarities test from WAIS-III and the phase-locking properties of 40 Hz ASSR in both patients with schizophrenia and controls. In addition, gamma-range ASSRs have also been shown to be positively associated with cognitive performance on two other tests measuring the complex information processing speed in healthy individuals, the Trial making test (MCCB) test (Sun et al., 2018) and the Symbol coding (WAIS-III) (Rass et al., 2012). The results of Sun et al. (2018) and Rass et al. (2012) are also consistent with studies of healthy individuals, which show that individuals with better phase

synchronisation between brain regions perform more efficiently on tasks measuring cognitive ability (Churchill et al., 2021; Neubauer and Fink, 2009). Thus, the fact that the 40 Hz and IGF frequency responses were negatively correlated with the mean response time in the ToL (PEBL-Lt) task is in line with findings reported by other researchers in the literature, which show that individuals with higher synchronisation of gamma frequency responses perform reasoning ir problem-solving tasks better.

## 5.2.3 General discussion of the results of both studies

Taken together, the results of these studies suggest that the links between gamma-range ASSR and cognitive domains are not simple, but rather complex. In a cognitive study of 40 Hz ASSR and cognitive abilities, individuals who performed more ToL (PEBL-Lt) moves, and thus were less efficient on the task, had a stronger and more synchronised ASSR. On the other hand, in a second study on the correlations between IGFs and cognitive ability, 40 Hz and IGF frequency responses were negatively correlated with the mean response time in the ToL task (PEBL-Lt), so that faster task performers showed a stronger and more synchronised ASSR. A stronger gamma response may indicate over-activation of neural networks, which interferes with efficient ToL performance (Díez et al., 2014a). However, individuals with higher gamma frequency synchrony have been shown in other studies to perform reasoning and problem-solving tasks faster (Sun et al., 2018; Rass et al., 2012). The inconsistency of our results can be explained by the fact that the number of moves in the ToL task and the mean move time might reflect different aspects of the cognitive abilities used in the task, and the conflicting correlations of these measures with ASSR mean that subjects might have used different strategies to complete the task.

In particular, the different indices for the ToL task reflect the different abilities of the subjects to perform this task. Newman and Pittman (2007) found that that when there is only one possible solution to the ToL task, participants are more likely to choose the incorrect move and make more additional moves to correct it, thus increasing the total number of moves (Newman and Pittman, 2007). When more than one possible solution is available, the mean move time for initiating sub-goals increases as participants have to consider more options to achieve these sub-goals (Newman and Pittman, 2007). Finally, the research shows that longer pre-planning time results in fewer moves in ToL tasks for which there is only one optional solution (Newman and Pittman, 2007). Hence, the pre-planning time of a ToL

task is related to the number of moves, while the continuous planning time, i.e. the anticipation of sub-goals, is related to the mean move time. Hence, the pre-planning time of a ToL task is related to the number of moves, while the continuous planning time, i.e. the anticipation of sub-goals, is related to the mean move time. Thus, in our studies, the number of moves and the mean move time of the ToL task may reflect different aspects of the cognitive abilities used to solve ToL task and thus have different relationships with ASSRs.

Another study found that subjects use different tactics when performing ToL tasks. Cazalis et al. (2003) studied ToL (simplified version of ToL; Baker et al., 1996) tasks and brain activation in fMRI and found that standard performers manipulate information in working memory more intensively: greater activation of the anterior cingulate region suggests that they may have more difficulty resolving conflicts between important and unimportant items in the planning stages of subgoals, and therefore take more time to complete the task, and make more erroneous moves, than superior performers (Cazalis et al. 2003). Superior performers are more likely to identify critical elements of the task and to plan subgoals more efficiently, thus reducing their working memory load (Cazalis et al., 2003). This is also suggested by the greater activation of the DLPFC among superior performers, which is associated with more effective planning and strategy development skills (Cazalis et al., 2003). Thus, different strategies based on different cognitive abilities used by subjects during the ToL task may lead to different task performance. It is possible that the inconsistency in the associations between ToL task performance and ASSR indices found in our studies reflects the fact that subjects use different cognitive strategies when performing the ToL task.

Thus, the number of moves and the mean move time in ToL task may reflect different aspects of planning and working memory, and their correlation with ASSR may represent the activity of the different cognitive aspects in the frontal area. This overall result is generally in line with Ball et al. (2011) study. In this study, it was shown that coherent cortical neuronal bursts as assessed by BOLD are positively correlated with better performance on an n-back task requiring sustained attention and working memory. However, at the same time, coherent neuronal activity is also positively correlated with the number of errors on the Go/No-Go test, indicating poorer inhibition of the preparatory response (Ball et al., 2011).

## 5.2.4 Research limitations and recommendations for further studies

Based on the literature review, it was predicted that ASSR at 40 Hz and IGF would correlate with performance on more cognitive tasks (not only the ToL task) reflecting differences in information processing speed, and therefore semantic, spatial, arithmetic and lexical aspects of information processing were assessed. However, no links other than the relationship between the ASSR and the ToL task have been identified. However, it should be noted that in previous studies, the correlation between ASSR and tasks assessing information-processing abilities was most pronounced in patients with cognitive impairments such as schizophrenia (Tada et al., 2016) or multiple sclerosis (Arrondo et al., 2009). This suggests that these correlations may only exist in clinical groups with cognitive deficits and/or that the correlations may depend on other characteristics of the subject groups considered.

The assumption that the correlations may depend on characteristics of the subject groups considered is supported by the fact that the results of the two studies on the correlation between ToL task and gamma-band ASSRs did not completely overlap, even though similar stimulation methods and the same analysis and evaluation parameters were used. The 40 Hz ASSR study involved only men, while the second, individual frequency study involved a mixed group of men and women to make the sample more representative of the population. ASSR in women may be influenced by hormonal fluctuations (Griškova-Bulanova et al., 2014; Melynytė et al., 2018). In addition, other studies using the same methodologies but with different groups of subjects have obtained different results (among Rass et al. (2010) and Rass et al. (2012) and among Light et al. (2006) and Kirihara et al. (2012)). Thus, future ASSR studies must take into account the characteristics of the subjects.

On the other hand, no correlations of ASSRs with other tasks were found possibly because only auditory stimulation was used. Although auditory stimulation elicits the strongest EEG responses in the gamma range and is widely used in studies of this nature (Edgar et al., 2017; Galambos et al., 1981; Giani et al., 2012), however, it is not known with certainty whether the auditory modality is optimal for determining gamma activity characteristics (Picton et al., 2003b). In addition, the relationship between ASSRs and information processing speed may depend on the sensory-task modality compatibility, i.e., the auditory response is related to the performance of the auditory task (this is in line with the results of the studies by Baltus and Herrmann (2015), Purcell et al. (2004) and Molina et al. (2020)). However, most of the cognitive tasks used by us and other researchers are related to the visual modality. Therefore, further studies should include stimuli and/or cognitive tasks from other modalities to investigate the effects of the sensory modality.

Finally, the methods used to estimate ASSRs may have influenced the results. In the study on the relationship between IGFs and cognitive abilities, the correlations of ASSR with ToL were only calculated for measurements in the central region. This area is the most commonly used for determining ASSR correlations with cognitive ability (e. g., Kirihara et al., 2012; Rass et al., 2012; Tada et al., 2016), in contrast to the left and right-side areas. However, for example, Díez et al. (2014a; 2014b) found an association between lateralized responses in their groups. Thus, in future studies, lateral positions should also be considered when assessing ASSRs.

# 6. CONCLUSIONS

- A systematic review of the literature revealed that individual differences in the gamma-range ASSRs might reflect abilities to control attention and temporarily store and process information.
- The event-related power perturbation and phase-locking of 40 Hz ASSR positively correlated with the mean number of steps on the Tower of London task in a sample of young, healthy males.
- The event-related power perturbation and phase-locking of the envelopefollowing response at the 40 Hz and IGF negatively correlated with the performance speed on the Tower of London task.

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# PUBLICATIONS

### Publications included in the thesis

- Parčiauskaitė, V., Voicikas, A., Jurkuvėnas, V., Tarailis, P., Kraulaidis, M., Pipinis, E., and Griškova-Bulanova, I. "40-Hz Auditory Steady-State Responses and the Complex Information Processing: An Exploratory Study in Healthy Young Males." PloS One, Vol. 14, No. 10, 2019, p. e0223127. <u>https://doi.org/10.1371/journal.pone.0223127</u>.
- Parčiauskaitė, V., Bjekić, J., and Griškova-Bulanova, I. "Gamma-Range Auditory Steady-State Responses and Cognitive Performance: A Systematic Review." Brain Sciences, Vol. 11, No. 2, 2021, p. 217. <u>https://doi.org/10.3390/brainsci11020217</u>.
- Parčiauskaitė, V., Pipinis, E., Voicikas, A., Bjekić, J., Potapovas, M., Jurkuvėnas, V., and Griškova-Bulanova, I. "Individual Resonant Frequencies at Low-Gamma Range and Cognitive Processing Speed." Journal of Personalized Medicine, Vol. 11, No. 6, 2021, p. 453. <u>https://doi.org/10.3390/jpm11060453</u>.

### Conferences on the thesis topic

- Poster presentation: Parčiauskaitė V., Voicikas A., Jurkuvėnas V., Tarailis P., Kraulaidis M., Pipinis E., and Griškova-Bulanova I. "40 Hz auditory steady-state early latency response is related to the Stroop task performance". 11th Conference of the Lithuanian Neuroscience Association, Vytautas Magnus University, Kaunas, Lithuania; 29 November 2019.
- Poster and oral presentation: V. Parčiauskaitė, A. Voicikas, P. Tarailis, M. Kraulaidis, V. Jurkuvėnas, I. Griškova-Bulanova "40 Hz ASSR relation to cognitive performance". 10th Conference of the Lithuanian Neuroscience Association, Life Sciences Centre, Vilnius University, Vilnius, Lithuania; 30 November – 1 December 2018.

 Poster presentation: Parčiauskaitė V., Tarailis P., Kraulaidis M., Voicikas A. ir Griškova-Bulanova I. "40 Hz steady-state responses and individual sensory preference". 7th International Conference "Aspects of Neuroscience", Faculty of Biology, University of Warsaw, Warsaw, Poland; 24-26 November 2017.

## Other publications

 Dankinas, D., Parčiauskaitė, V., and Dapšys, K. "Intra-Individual Reaction Time Variability and Response Preparation: An EEG Study." Acta Neurobiologiae Experimentalis, Vol. 75, No. 4, 2015, pp. 462–468. <u>https://pubmed.ncbi.nlm.nih.gov/26994424/</u>

## Other conferences

- Poster presentation: Parčiauskaitė V., Tarailis P., Kraulaidis M., Voicikas A. ir Griškova-Bulanova I. "40 Hz steady-state responses and individual sensory preference". 9th Conference of the Lithuanian Neuroscience Association, Lithuanian University of Health Sciences, Kaunas, Lithuania; 1 December 2017.
- Poster presentation: Parčiauskaitė V., Voicikas A. ir Griškova-Bulanova I. "Auditory steady-state responses to stimulation of different presentation order and duration". 8th Lithuanian Neuroscience Association Conference, Life Sciences Centre, Vilnius University, Vilnius, Lithuania; 9 December 2016.
- Oral presentation: Parčiauskaitė V. "Brainwave entrainment". Lithuanian Young Scientists' Union Scientific Camp "Smithy of Ideas 2017", University of Applied Sciences, Valmiera, Latvia; 19-21 May 2017.
- Poster presentation: Parčiauskaitė V., Voicikas A. ir Griškova-Bulanova I. "Auditory steady-state responses to stimulation of different duration".
   6th International Conference "Aspects of Neuroscience", Faculty of Biology, University of Warsaw, Warsaw, Poland; 25-27 November 2016.

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## NOTES

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