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Does brain ability to synchronize with 40 Hz auditory stimulation change with age?

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Auditory steady-state responses (ASSRs) are widely applied to test brain ability to follow external stimulation and this appeared to be a promising method in neuropsychiatric disorders. Nevertheless, there is no established conclusion on the way aging affects phase-locking measures of ASSRs in healthy subjects. We aimed to identify the effects of aging on phase-locking measures of 40 Hz ASSR. The effect of aging was tested in a sample of 46 healthy male subjects (20–58 years old) during eyes open condition. Stimuli were 500 ms trains, consisting of 20 identical clicks (1.5 ms burst of white noise) delivered binaurally. Time-frequency analysis of the data was performed and phase-locking index, evoked amplitude and total intensity measures were extracted and decomposed by non-negative multi-way factorization. As shown by curve-fitting analyses, phase-locking index and evoked amplitudes were diminishing with age in the linear manner. This was also proven by ANOVA testing when sample was divided into age groups. No effect of age on the total intensity was found. The complexity of the factors modulating the 40 Hz ASSR is not entirely solved; nevertheless, the current results suggest that the ability to synchronize to high frequency external stimulation diminishes with age. This should be taken into account, particularly when ASSRs are used in clinical practice, comparing patients and healthy subjects.

Key words: auditory steady-state response, age, time-frequency analysis, phase-locking index

The auditory steady-state response (ASSR) is observed when stimuli are presented periodically resulting in electroencephalographic entrainment (Picton et al. 2003). The frequency of the ASSR is close to the frequency of stimulation and the greatest magnitude is observed when stimuli are presented at 40 Hz (Galambos et al. 1981). The source of ASSR has been localized in the primary auditory cortex, supratemporal gyrus, brainstem with additional activity arising from cerebellum (Makela and Hari 1987, Hari et al. 1989, Pantev et al. 1996, Pastor et al. 2006). Since its discovery in 1981, ASSRs have been employed by physiologists, psychologists, and physicians along with transient event-related potentials (ERPs); however, both types of EEG responses serve different functions.

Predominately, ASSRs are used for testing hearing sensitivity or as a marker of the state of consciousness during anesthesia (Picton et al. 2003). But the gamma range ASSR (especially in the case of 40 Hz ASSR) has also been used as an index of the ability for gamma band frequency generation in local cortical networks in neuropsychiatric disorders: schizophrenia (Kwon et al. 1999, Hong et al. 2004, Light et al. 2006, Brenner et al. 2009, Griskova-Bulanova et al. 2013), bipolar disorder (O'Donnell et al. 2004, Rass et al. 2010, Oda et al. 2012) and Alzheimer's disease studies (Osipova et al. 2006, van Deursen et al. 2009).

Obviously, different groups of patients may substantially differ in their age, and part of the changes observed might be age-related. Nevertheless, there is no established conclusion on aging effects on ASSRs in healthy subjects. Some studies focused on ASSR development from childhood to adolescence, reporting amplitude increase of ASSR with age (Rojas et al. 2006, Poulsen et al. 2009, Herdman 2011). Research in adult subjects of various age gave inconsistent results, some reporting no effect of age on auditory ASSRs (Johnson et al. 1988, Boettcher et al. 2001, Rojas et al.

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2006), other finding ASSR amplitude increase with increasing age (Boettcher et al. 2002, Poulsen et al. 2007). Importantly, various analyses methods and estimated parameters do not allow directly comparing the results from various studies. Likewise, phase-locking of the 40 Hz ASSR was not evaluated in any of the studies, although this measure is frequently used and has proven to be informative in clinical researches (Light et al. 2006, Osipova et al. 2006, van Deursen et al. 2009, Rass et al. 2010, 2012, Oda et al. 2012) together with amplitude measures. Thus, we aimed to identify, what are the effects of aging on wavelet extracted phase-locking index and amplitude measures of 40 Hz ASSRs from healthy subjects.

Forty six male subjects were investigated. Only right-handed male subjects were chosen to avoid possible effects of hormonal fluctuations on the ASSRs. The subjects had no history of psychiatric or neurologic disorders and no history of any addiction except for tobacco. Subjects were asked to refrain from smoking for two hours before the experiment and do not consume caffeine-containing drinks. All subjects showed normal binaural auditory thresholds. Informed consent was obtained, as approved by the Ethics Committee of the Republican Vilnius Psychiatric Hospital.

Stimuli were 500 ms trains, consisting of 20 identical clicks (1.5 ms burst of white noise) (interspersed with 20 and 10 Hz stimuli – data not reported here), delivered binaurally through headphones (peak SPL of 60 dB). The 40 Hz trains were presented sixty times in a pseudo-random order with an inter-train interval of 1–1.5 s.

Participants were instructed to let their thoughts wander during the presentation of auditory stimuli and to fix their gaze at a fixation cross approximately 1.5 m in front of them. A recording run lasted about 4 minutes.

The EEG was recorded with a digital EEG device (Galileo Mizar, by EBNeuro, Italy) from F3, Fz, F4,C3, Cz, C4, P3, Pz and P4 sites (10/20 International system) using Ag/AgCl electrodes. Averaged earlobe electrodes served as a reference; the ground electrode was attached to the forehead. The impedance was kept below 5 kO. Data was digitized at 512 Hz.

Off-line processing was performed in ERPWAVELAB and EEGLAB for MatLab (Delorme and Makeig 2004, Morup et al. 2006, 2007). Wavelet transformation (WT; complex Morlet wavelet from MatLab Wavelet Toolbox; frequencies represented from 10 to 80 Hz, 1 Hz intervals between each frequency) was performed. The wavelet transformed evoked potential measure (evoked amplitude, corresponding to phase-synchronized WT amplitude measure) and phase-locking index (phase locking factor of the evoked oscillations from trial to trial ranging from 0 (random phase) to 1 (nearly identical phase) were analyzed (Morup et al. 2006). Additionally, the average amplitude of the oscillation (both non-phase-locked and phase-locked) was investigated to obtain a measure of the total intensity increase induced by the stimuli. Prior to WT, 10% of the epochs with the largest variability were rejected in the dataset of each subject/condition. The baseline correction was made by the extraction of random evoked amplitude and phase synchronization activity, which was estimated by calculating the mean of artificially generated random evoked amplitude and phase synchronization samples (Morup et al. 2006).

Individual time–frequency representations of evoked amplitude, phase-locking index and total intensity across all channels were created. It follows that the subject-specific strength to the activity that is most common across subjects was extracted through non-negative multi-way factorization (NMWF) (Morup et al. 2006, 2007). The application of NMWF creates time–frequency plots of the evoked amplitude, phase locking factor and total intensity at the same time indicating how the parameter varies with experimental manipulation. In other words, the multi-subject NMWF analysis of the 3-way array of channel × time-frequency × subject gives the subject-specific strength to the activity that is most common across subjects, i.e. creates a subject-weighted collapse and makes it possible to quantify (by giving the single estimation of the measure of interest) how the measure of interest varies with experimental manipulation for all the subjects (Morup et al. 2007). This has proven useful in the analysis of event-related potentials (Arnfred et al. 2007, 2008, Griskova-Bulanova et al. 2012) and in the analysis of ASSRs (Griskova-Bulanova et al. 2011, 2013). The window for mathematical decomposition of ASSRs was set as 30–46 Hz and 0 to +500 ms.

In order to evaluate the change in measurements with age, linear regression analysis was performed. Further, subjects were arbitrary divided into groups based on their age in 10 years steps: 20–30 years group (n=13), 30–40 years group (n=13), 40–50 years group (n=9) and 50–60 years group (n=11). Univariate analysis of vari-

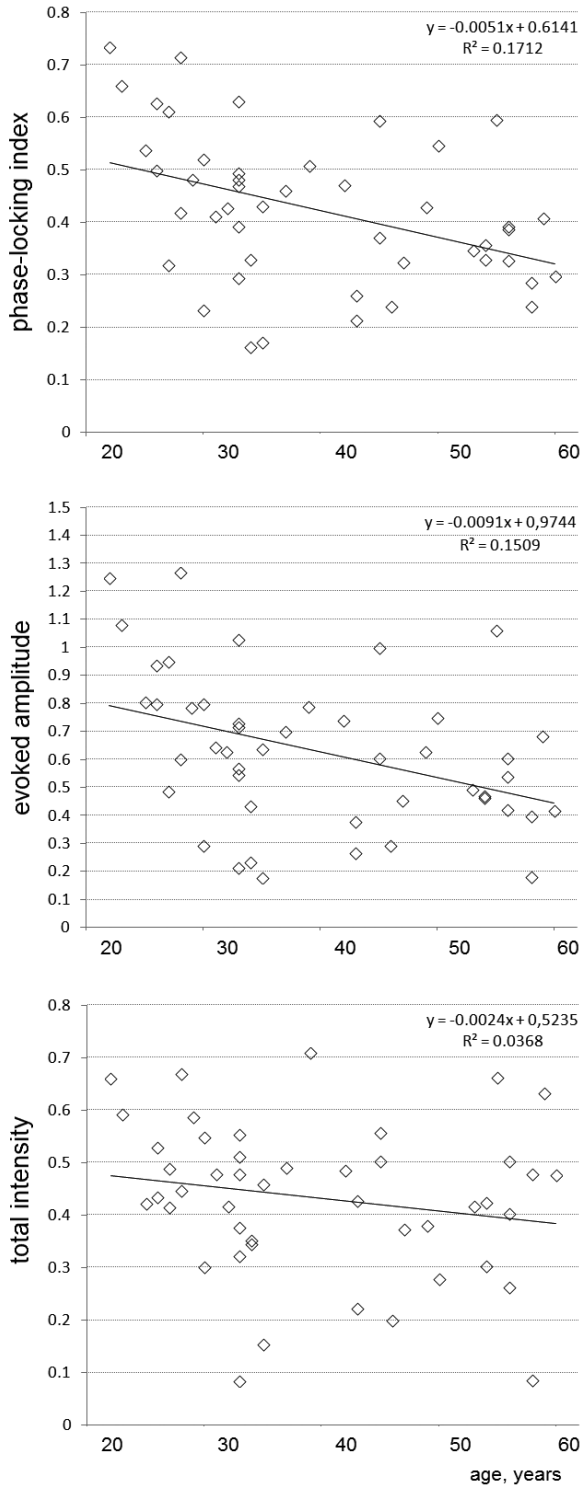

Fig. 1. Scatter plots of 40 Hz ASSR phase-locking index, evoked amplitude and total intensity values *versus* subjects' age

ance (ANOVA) was performed, testing the effect of age group as a factor. *Post-hoc* analyzes were performed using Least Significant Difference (LSD) test.

ASSRs were detected for all subjects. In line with previous studies, the non-negative multi-way factorization decomposition of selected measures of ASSRs resulted in the observation of a single component, maximal over Cz at about 230 ms and 38–40 Hz following 40 Hz stimulation (40 Hz ASSR) (Griskova-Bulanova et al. 2011, 2013).

Linear regression analysis was performed to test relationship between subjects' age and phase-locking index values, evoked amplitude values and total intensity values. Curve-fit analyses revealed a small but significant linear decrease in the phase-locked 40 Hz ASSR measures as a function of age (Fig. 1): R^2=0.171, $F_{1,44}$=9.091, P=0.004 for phase-locking index and R^2=0.151, $F_{1,44}$=7.820, P=0.008 for evoked amplitude. No significant relationship with subjects' age for the total intensity values was found. Means and standard deviations of phase-locking index values, evoked amplitude values and total intensity of all four age groups are presented in Table I. Univariate ANOVA indicated that age group factor was significant for phase-locking index values ($F_{3,43}$=3.595, P=0.021, observed power 0.753). *Post-hoc* testing revealed that phase-locking index values were significantly larger in 20–30 years old group as compared to other groups (P<0.05). Head plot of phase-locking index collapsed across subjects for the 40 Hz ASSR, time-frequency plots as a weighted collapse across subjects and electrodes for the 40 Hz ASSR and means and standard deviations of NMWF scores of phase-locking index for the 40 Hz ASSR in 20–30, 30–40, 40–50 and 50–60 years old age groups are presented in Figure 2.

As revealed by univariate ANOVA, age group factor was significant for evoked amplitude measures ($F_{3,43}$=3.685, P=0.019, observed power 0.764). As indicated by *post-hoc* testing evoked amplitude values were significantly larger in 20–30 years old group as compared to all other groups (P<0.05). No effect of age group on total intensity values was found ($F_{3,43}$=1.739, P=0.174).

The major finding of the current study is that phase-locked measures of 40 Hz ASSR – phase-locking index and evoked amplitude – are diminishing with age. To our knowledge, this is the first study implementing routinely used phase-locking measures and assessing their relationship to subjects' age.

Table I

Means and Standard deviations of phase-locking index, evoked amplitude and total intensity of the 40 Hz ASSR in 20–30 years, 30–40 years, 40–50 years and 50–60 years old groups

	20–30 years	30–40 years	40–50 years	50–60 years
Phase-locking index				
Mean	0.52	0.40	0.38	0.36
SD	0.15	0.13	0.14	0.09
Evoked amplitude				
Mean	0.82	0.57	0.57	0.52
SD	0.28	0.25	0.24	0.22
Total intensity				
Mean	0.51	0.40	0.38	0.42
SD	0.11	0.16	0.13	0.16

Functionally, pronounced effect of aging has been shown on ERPs, increasing amplitudes of P1–N1–P2 sensory complex (Anderer et al. 1996, Bertoli and Probst 2005), reducing amplitudes of cognitive components and elongating latencies (Knight 1987, Gaeta et al. 1998, Gall et al. 2007).

In the past years, ASSRs received much attention as an index of brain ability to synchronize to external stimulation; with synchronization reaching maximum at about 200 ms post stimulus at the frequency of 40 Hz (Rojas et al. 2006, Griskova-Bulanova et al. 2013). However, studies, addressing age-related changes of brain ability to synchronize to external stimulation in healthy adult subjects are relatively sparse, presenting inconclusive results. In the first study by Johnson and coworkers (1988), no significant differences in phase or amplitude of the 40 Hz ASSRs between the two age groups – younger (38 years) and elderly (70 years) were found; however, very small samples (7 and 5 subjects) were investigated (Johnson et al. 1988). Similarly, no age effect on the amplitudes and phases was found by Boettcher and colleagues (2001) when amplitude-modulation rate was 40 Hz and on amplitudes in the study by Purcell and others (2004) when white noise was modulated at frequencies from 30 Hz to 50 Hz. Rojas and coauthors (2006), applying MEG, showed that 40 Hz ASSR power related to age and this relationship was best described by exponential regression. However, Rojas and colleagues (2006) included subjects from 5 to 52 years old. Relationship between ASSR relative power and age between 20 to 50 years was stable, indicating no changes in power with

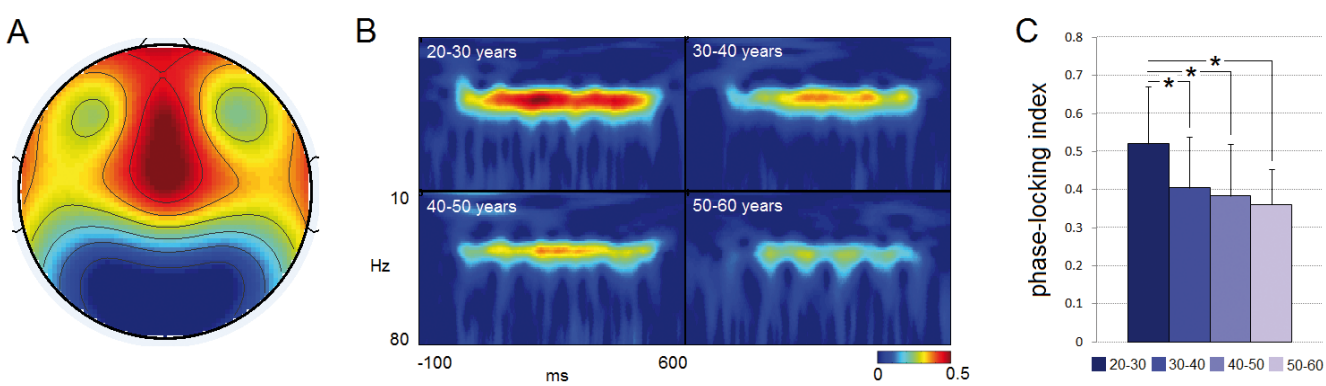

Fig. 2. (A) Head plot of phase-locking index collapsed across subjects for the 40 Hz ASSR. (B) Time-frequency plots as a weighted collapse across subjects and electrodes for the 40 Hz ASSR in 20–30, 30–40, 40–50 and 50–60 years old age groups. (C) Means and standard deviations of NMWF scores of phase-locking index for the 40 Hz ASSR in 20–30, 30–40, 40–50 and 50–60 years old age groups. *P<0.05.

increasing age (Rojas et al. 2006). On the contrary, Boettcher and coworkers (2002) have shown larger amplitudes of 38 Hz frequency-modulated ASSR in aged subjects. Poulsen and others (2007), showed a small, but significant, linear increase in the amplitude of the 40 Hz ASSR as a function of age in adults from 19 to 45 years of age. This was accompanied by a decrease in ASSR variability with age (Poulsen et al. 2007).

The results by Boettcher and coauthors (2001) and Rojas and others (2006) are partially in line with our observation of no significant aging effect on total intensity measure. Whereas amplitude measure used by Poulsen and colleagues (2007) is different from the one we used. Importantly, no of the studies mentioned above implemented phase-locking measures that would be comparable to widely and routinely used phase-locking index measure that is the least sensitive to the noise (Kalcher and Pfurtscheller 1995, Griskova et al. 2007, 2009).

Functionally, synchronous oscillations and particularly ASSRs in the gamma frequency range were related to GABAergic transmission (Lewis et al. 2008, Lewis et al. 2005, Whittington et al. 2000). This process is believed to be mediated *via* both interneuron–interneuron and interneuron–pyramidal neuron cell connections. Synchronization is hypothesized to be propagated through networks in a cycle of GABA(A)--mediated inhibition followed by rebound excitation and then inhibition (Gonzalez-Burgos and Lewis 2008). Several pharmacological studies supported GABA participation in the regulation of the 40 Hz ASSR, as administration of the GABA agonists temazepam and propofol attenuates the 40 Hz ASSR (Jaaskelainen et al. 1999, Plourde et al. 2008). Moreover, GABAerging transmission has shown to be involved in conditions where changes in ASSRs occur: reduced ASSRs in schizophrenia and bipolar disorder were associated with up-regulation of GABAergic system (Brambilla et al. 2003, Deng and Huang 2006) and enhanced ASSR in Alzheimer disease were related to disinhibition of GABAergic system (Di Lazzaro et al. 2004, Limon et al. 2012). Noteworthy, decrease in GABAergic parameters with age has been reported (Tohgi et al. 1993, Krzywkowski et al. 1996). Recently, it has been shown that auditory cortex shows age-related decreases in pre-synaptic markers for GABA. Caspary and others (2013), suggested that age-related changes in GABA(A)R subunit composition would alter the magnitude and temporal properties of inhibitory synaptic transmission and could underpin observed age-related functional changes seen in the elderly.

We speculate that diminishing phase-synchronization of 40 Hz ASSRs with age might be related to changes mediated by GABAergic system. The complexity of the factors modulating the 40 Hz ASSR is not entirely solved; nevertheless, the current results suggest that the ability to synchronize to high frequency external stimulation diminishes with age. This should be taken into account, particularly when ASSRs are used in clinical practice, comparing patients and healthy subjects.

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