

Title:

Introducing Rhythmic Sinusoidal Amplitude-Modulated Auditory Stimuli with Multiple Message Frequency Coding for Fatigue Reduction in Normal Subjects: An EEG Study

Abbreviated title:

Rhythmic Multi-Message SAM Stimuli Reduces Fatigue

Author names and affiliations:

Elham Shamsi,^{1,2} Ahmadreza Keihani,^{1,2} Zahra Shirzhiyan,^{1,2} Morteza Farahi,^{1,2} Amin Mahnam,³ Mohsen Reza Heydari,⁴ and Amir Homayoun Jafari^{1,2}

¹Department of Medical Physics and Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran, ²Research Center for Biomedical Technologies and Robotics, Tehran University of Medical Sciences, Tehran, Iran, ³Department of Biomedical Engineering, Faculty of Engineering, University of Isfahan, Isfahan, Iran, ⁴Department of Neurology, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran

Corresponding author: Amir Homayoun Jafari, Department of Medical Physics and Biomedical Engineering, School of Medicine, Tehran University of Medical Sciences, Poursina Street, Ghods Street, Keshavarz Boulevard, Tehran, Iran. E-mail: h_jafari@tums.ac.ir.

Number of total pages: 29

Number of figures: 7

Number of tables: 4

Number of words for Abstract: 250 (including “Abstract” and all the key words)

Number of words for Significance Statement: 110 (including “Significance Statement”)

Number of words for Introduction: 650 (including “Introduction” and citations)

Number of words for Discussion: 1372 (including ‘Discussion’ and citations)

Conflict of interest: The authors declare no competing financial interests.

Acknowledgements: This work was supported by a grant from the deputy of the research review board and the ethics community of Tehran University of Medical Sciences (Grant NO: 30863)

1 **Abstract**

2 Many of the brain-computer interface (BCI) systems depend on the user's voluntary eye movements.
3 However, voluntary eye movement is impaired in people with some neurological disorders. Since their
4 auditory system is intact, auditory paradigms are getting more patronage from researchers. However, lack of
5 appropriate signal-to-noise ratio in auditory BCI necessitates using long signal processing windows to
6 achieve acceptable classification accuracy at the expense of losing information transfer rate. Because users
7 eagerly listen to their interesting stimuli, the corresponding classification accuracy can be enhanced without
8 lengthening of the signal processing windows. In this study, six sinusoidal amplitude-modulated auditory
9 stimuli with multiple message frequency coding has been proposed to evaluate two hypotheses: 1) these
10 novel stimuli provide high classification accuracies (greater than 70%), 2) the novel rhythmic stimuli set
11 reduces the subjects' fatigue compared to its simple counterpart. We recorded EEG from nineteen normal
12 subjects (twelve female). Five-fold cross-validated naïve Bayes classifier classified EEG signals with respect
13 to power spectral density at message frequencies, Pearson's correlation coefficient between the responses
14 and stimuli envelopes, canonical correlation coefficient between the responses and stimuli envelopes. Our
15 results show that each stimuli set elicited highly discriminative responses according to all the features.
16 Moreover, compared to the simple stimuli set, listening to the rhythmic stimuli set caused significantly lower
17 subjects' fatigue. Thus, it is worthwhile to test these novel stimuli in a BCI experiment to enhance the number
18 of commands and reduce the subjects' fatigue.

19 *Key words:* rhythm; amplitude modulation; multiple message frequency coding; classification; fatigue

20 **Significance Statement**

22 Auditory BCI users eagerly listen to the stimuli they are interested in. Thus, response classification accuracy
23 may be enhanced without the need for trial lengthening. Since humans enjoy listening to rhythmic sounds,
24 this study was carried out for introducing novel rhythmic sinusoidal amplitude-modulated auditory stimuli
25 with multiple message frequency coding. Our results show that each stimuli set evoked reliably
26 discriminative responses according to all the features, and rhythmic stimuli set caused significantly lower
27 fatigue in subjects. Thus, it is worthwhile to test these novel stimuli in a BCI study to increase the number
28 of commands (by N^N permutations of just N message frequencies) and reduce the subjects' fatigue.

30 **Introduction**

31 Brain-computer interfaces (BCI) makes muscle-independent communication between brain
32 and computer possible. Thus, translating the user's intention to an external command (e.g.,
33 wheelchair control) comes true (Wolpaw et al., 2002). BCI can improve the quality of life for
34 people with motor disabilities. Electroencephalogram (EEG) has been considered a reliable
35 modality for using in BCI studies due to its noninvasiveness, good temporal resolution, easy
36 implementation, and low cost (Wang et al., 2004; Hoffmann et al., 2008; Nijboer et al., 2008).

37 Patients with some neurological disorders, such as late-stage amyotrophic lateral sclerosis
38 (ALS) and minimally conscious state (MCS), cannot perform voluntary eye movements or
39 fixate their gaze. Moreover, daily usage of tactile BCI is hard because most people do not have
40 tactile stimulators at home (Kaufmann et al., 2013). Thus, there has been an increasing interest
41 towards auditory BCI (aBCI) (Hill et al., 2004; Kanoh et al., 2008; Nijboer et al., 2008; Furdea
42 et al., 2009; Klobassa et al., 2009; Kübler et al., 2009; Halder et al., 2010; Schreuder et al.,
43 2010; Higashi et al., 2011; Höhne et al., 2011; Kim et al., 2011; Schreuder et al., 2011; Kim et
44 al., 2012; Lopez-Gordo et al., 2012; Käthner et al., 2013; Nakamura et al., 2013; Simon et al.,
45 2014; Kleih et al., 2015; Zhou et al., 2016; Heo et al., 2017; Kaongoen and Jo, 2017), which
46 uses auditory selective attention to influence event-related potentials (ERPs) and auditory
47 steady-state responses (ASSRs). ASSR is chiefly evoked by listening to amplitude-modulated
48 (AM) tones, and its spectrum has peaks at message frequency (f_m) (Picton et al., 2003; Lopez
49 et al., 2009; Tanaka et al., 2013; Tanaka et al., 2015).

50 In aBCI, lengthening the processing window enhances the classification accuracy, but it
51 reduces the speed (Lopez-Gordo et al., 2012). However, because the users eagerly listen to
52 their interesting stimuli, the classification accuracy is enhanced (Zhou et al., 2016; Heo et al.,
53 2017). Moreover, rhythmic stimulation modulates the intrinsic neural oscillatory
54 characteristics (Herrmann et al., 2016). Rhythmic sinusoidal AM tones elicited EEG (Heo et

55 al., 2017; Shamsi et al., 2017) and MEG (Kuriki et al., 2013), but each of those stimuli had just
56 one message frequency. Further, responses were not classified in (Kuriki et al., 2013) and
57 subjects` fatigue were not evaluated in (Kuriki et al., 2013; Heo et al., 2017).

58 To our knowledge, there is not any research on AM sequences with multiple message
59 frequencies. In this paper, six novel stimuli with multiple message frequency coding were
60 introduced to test our hypotheses: 1) the resulting ASSRs are highly discriminative, and 2)
61 listening to the novel rhythmic set reduces the subjects` fatigue compared to the simple set.

62

63 **Materials and Methods**

64 **Subjects.** Nineteen healthy (twelve female) volunteers took part in this study. They all
65 participated in our previous study (Shamsi et al., 2017), too. Their age was in the range of 22-
66 29 years (25.26 ± 2.05). All of them were right-handed according to Edinburgh Handedness
67 Inventory (Oldfield, 1971) (Index: 0.75 ± 0.26). Participants reported no musical expertise. The
68 instructions were explained to them. Subjects signed written informed consent form before
69 conducting the experiments. All the procedures were approved by the ethics committee and the
70 deputy of research review board of Tehran University of Medical Sciences.

71 **Stimuli.** In order to maintain consistency with other ASSR studies, double-sideband
72 transmitted-carrier amplitude modulation with a modulation depth of 1 was used to generate
73 the stimuli (to get more details, see (Lopez et al., 2009; Kuriki et al., 2013; Tanaka et al., 2013;
74 Heo et al., 2017)):

75

$$s(t) = \sin(2\pi f_c t) (1 + \sin(2\pi f_m t)) \quad (1)$$

76

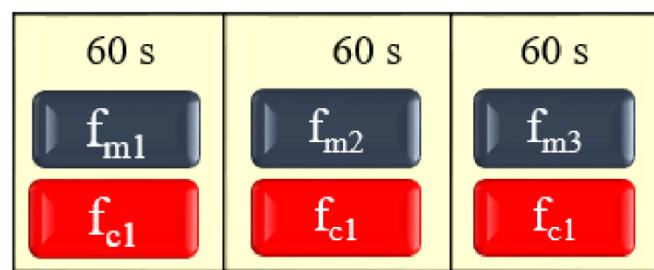
77 Where $s(t)$ stands for the stimulus signal. In addition, f_c and f_m are carrier and modulation (i.e.,
78 message) frequency, respectively. Two sets of stimuli were designed, each of which contained

79 three stimuli. All the stimuli had a duration of 180 s. Each stimulus comprised three f_{ms} . The
80 stimuli sets is schematically represented in **Figure 1**. Using multiple message frequencies in
81 each stimulus enriches its spectral content, because each f_m can elicit its corresponding peak in
82 ASSR spectrum. In this way, different orderings and permutations of f_{ms} make it possible to
83 produce various commands in aBCI. That is to say, using this coding, only N message
84 frequencies can generate N^N permutations, which means N^N stimuli and N^N commands,
85 whereas N^N message frequencies in single-message sinusoidal AM tones are required for
86 generating the same number of stimuli and commands. This is important because there is
87 limitation for message frequency selection in the sense that strong ASSRs were elicited by
88 message frequencies in the range of [30-50] Hz (Picton et al., 1987), so using multiple message
89 frequency coding facilitates the construction of stimuli corresponding to possible commands.

90 It is noteworthy that in this paper, whenever only a single carrier was present in the stimuli,
91 those stimuli are called “simple”, while the stimuli containing more than one carrier are referred
92 to as “rhythmic”. In other words, “rhythm” was generated using multiple carriers. For both sets
93 of stimuli, f_{ms} were chosen to be among the (30, 35, 40) Hz. This is because consistent and
94 robust ASSRs were elicited by message frequencies in the range of [30-50] Hz (Picton et al.,
95 1987). Carrier frequencies were selected among the musical notes to be interesting for the
96 subjects to listen to them. In this way, f_{cs} were members of the (262, 392, 494) Hz
97 corresponding to “do”, “sol”, and “si” musical notes, respectively. For the rhythmic stimuli,
98 the presence of each carrier was set to 0.5 s according to the best tempo sensitivity time interval
99 (Drake and Botte, 1993). Frequency details are displayed in **Table 1**. Each stimuli set contained
100 ascending, descending, and one of the possible zigzagging codings of message/carrier
101 frequency. In other words, within each set, we constructed only three permutations (out of 27

102

103

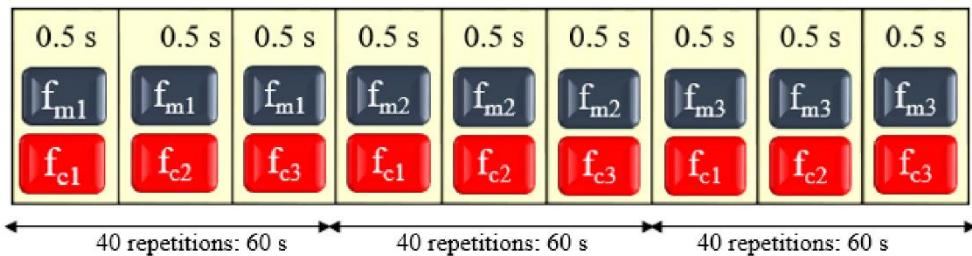


104

105

106

B



107

108 **Figure 1.** Schematic representation of the stimuli sets. **A**, simple set. **B**, rhythmic set.

109

110 possible permutations). For instance, a pattern with 30-30-35 Hz (two identical f_{ms} at first and
111 second portions of the triple pattern) or any similar permutation was not constructed. The
112 reason is that we wanted to see the distinguishability that all of 30, 35 and 40 Hz within the
113 proposed coding can provide in the corresponding ASSRs. Therefore, the presence of all three
114 f_{ms} in the proposed coding was required in this study. All the stimuli were generated in
115 MATLAB R2016b (MathWorks Inc., Natick, MA, USA). Sampling frequency for all the
116 stimuli was 4410 Hz.

117

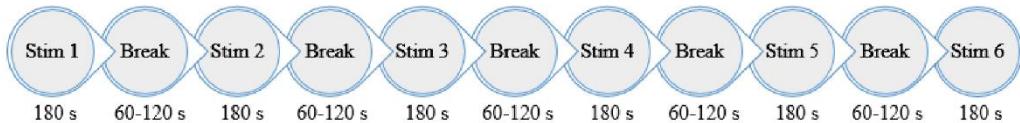
118

119 **Table 1. Message and carrier frequency details in the stimuli sets**

		Frequency (Hz)					
		f_{m1}	f_{m2}	f_{m3}	f_{c1}	f_{c2}	f_{c3}
Stimuli name							
Simple set	SA	30	35	40	262	-	-
	SB	40	35	30	494	-	-
	SC	40	30	35	392	-	-
Rhythmic set	RA	30	35	40	494	262	392
	RB	40	35	30	262	392	494
	RC	40	30	35	494	392	262

120

121 **Task.** In order to assess the subjects` level of some psychological factors (i.e., depression,
122 stress, anxiety) through the week before the experiment, they were asked to fill DASS
123 questionnaire (Lovibond and Lovibond, 1995) preceding the stimuli presentation. Also, the
124 subjects filled questionnaire of current motivation (QCM) (Rheinberg et al., 2001; Vollmeyer
125 and Rheinberg, 2006) before the beginning of the experiment. In this way, it was possible to
126 measure their motivation and interest for participation, sense of challenge about the task, and
127 anxiety they feel about the task. Then, the participants were requested to remain eyes-closed,
128 still, and listen to the stimuli. For preventing from effects of the stimuli presentation order on
129 the reported fatigue, the stimuli were presented in a random order for each participant. In other
130 words, stimuli presentation order differed between the subjects. After listening to each
131 stimulus, participants reported the amount of stimulus-induced fatigue that they experienced,
132 as an integer number from 0 (minimum fatigue) to 10 (maximum fatigue) according to the
133 visual analog scale (VAS) and they were given a short break of 60-120 seconds before
134 presentation of the next stimulus. This procedure was performed for every stimulus. There were
135



136
137 **Figure 2.** Stimuli presentation procedure. “Stim” is the abbreviation of stimulus. The stimuli were presented in a
138 random order. After listening to each stimulus, which was 180 s long, the subjects reported the level of stimulus-
139 induced fatigue that they experienced, as an integer number from 0 (minimum fatigue) to 10 (maximum fatigue)
140 according to VAS. Then, they were given a short break of 60-120 s before presentation of the next stimulus.

141
142 two reasons for this separate presentation: 1) we wanted to ensure that the stimuli in each set
143 (i.e., simple, rhythmic) elicit sufficient inherently distinguishable responses in the brain, 2) we
144 wanted to measure the amount of fatigue that each stimulus caused to each subject, so we had
145 to present the stimuli separately (i.e., one by one). The stimuli presentation procedure is
146 displayed in **Figure 2**. It is worth mentioning that all the previously mentioned psychological
147 data were later used to explore whether there is a relationship between those factors and the
148 fatigue level that subjects reported.

149 **Experiment apparatus and recording.** Insert earphones ER-3A (Etymotic Research, Elk
150 Grove Village, IL) presented the stimuli to the subjects. For each stimulus, the volume was set
151 according to equal loudness level contours at the standard ISO 226:2003.

152 Electrode placement was performed according to 10-20 international system. Active g.LADYbird
153 electrodes were placed on Fz, Cz, T7 and T8. The reason for selecting Fz was that it is shown that Fz
154 has the highest average amplitude of responses in subjects to whom a music is pleasant (Kayashima et
155 al., 2017). Three other channels were consistently used in a number of previous ASSR studies (Lopez
156 et al., 2009; Higashi et al., 2011; Kim et al., 2011; Heo et al., 2017; Shamsi et al., 2017). According to
157 (Heo et al., 2017; Shamsi et al., 2017), right earlobe and Fpz were considered as the reference and
158 ground, respectively. EEG was recorded by g.USBamp (g.tec Medical Engineering GmbH, Austria) at

159 a sampling frequency of 4800 Hz. Online filters consisted of a bandpass with a bandwidth of [0.5-2000]
160 Hz, and a notch with a center frequency of 50 Hz.

161 **Signal analysis.** Firstly, in order to detect ASSR, we explored that whether the amplitude
162 spectrum at f_m was larger than the mean+3×standard deviation (SD) of the amplitude spectrum
163 at frequencies in the range of (f_m-1 to f_m-5) and (f_m+1 to f_m+5) (Tanaka et al., 2015). Then,
164 prominent features (i.e., power spectral density (PSD), Pearson's correlation coefficient (PCC),
165 canonical correlation coefficient (CCC)) were extracted. Feature extraction and classification
166 were performed across every 20-s segment of the EEGs to be consistent with the relevant
167 literature and practical applications (Kim et al., 2011; Heo et al., 2017). All the analyses were
168 carried out in MATLAB R2016b (MathWorks Inc., Natick, MA, USA) on a laptop, which had
169 Intel® Core™ i7-2670QM CPU @ 2.20 GHz as its processor.

170 **Power spectral density.** Keeping in mind that PSD is a robust feature for analyzing ASSR,
171 it was computed (using amplitude spectrum at f_m and its adjacent frequencies in the range of
172 f_m-5-f_m-1 and f_m+1-f_m+5) according to the literature (Tanaka et al., 2013; Tanaka et al.,
173 2015), as follows:

174

$$\text{PSD}(f_m) = \frac{\sum |X(f_m-1:f_m+1)|^2}{\sum (|X(f_m-5:f_m-1)|^2 + |X(f_m+1:f_m+5)|^2)} \quad (2)$$

175

176 Where $|X(f_m)|$ is the amplitude spectrum of the brain response at frequency of f_m .

177 **Pearson correlation coefficient.** To investigate the amount of correlation between each
178 stimulus and its corresponding ASSR, Pearson's correlation coefficient was used, which,
179 through this paper, will be referred to as "PCC". As previously mentioned, the spectrum of this
180 response has a peak at the modulation frequency (f_m) (Tanaka et al., 2013; Tanaka et al., 2015),
181 which is exactly the same as the fundamental frequency of the stimulus envelope. Thus, PCC

182 was calculated for investigating the amount of correlation between each stimulus` envelope
183 (i.e., X) and the ASSR (i.e., Y) that stimulus elicited. It was calculated as follows:

184

$$\rho_{X,Y} = \frac{\text{cov}(X,Y)}{\sigma_X \sigma_Y} \quad (3)$$

185

186 Where $\text{cov}(X,Y)$, σ_X , and σ_Y are the covariance of the two signals, the standard deviation of X
187 and the standard deviation of Y, respectively. $\rho_{X,Y}$ has a value within the interval of [-1, 1].
188 Obviously, if there is not any linear relationship between X and Y, it will be zero.

189 **Canonical correlation coefficient.** This method seeks for a pair of linear combinations for
190 two signals in such a way that the correlation between two canonical signals being maximized.
191 In this way, pairs having linear combinations with the most linear correlation are chosen in a
192 way that the previously identified pairs are orthogonal to them. If the EEG is represented by X
193 and the stimulus envelope is considered to be Y, their projection vectors are denoted by $\tilde{x} =$
194 $w_x^T X$ and $\tilde{y} = w_y^T Y$, respectively. Solving the equation below, w_x and w_y can be obtained:

195

$$\max_{w_x, w_y} \rho = \frac{E(\tilde{x}\tilde{y}^T)}{\sqrt{E(\tilde{x}\tilde{x}^T)E(\tilde{y}\tilde{y}^T)}} \quad (4)$$

196

197 Where, ρ is called the canonical correlation coefficient.

198 **Classification.** There were two cases for the classification, one for the responses to simple
199 stimuli set, and the other for those of the rhythmic stimuli set. That is to say, in this study, two
200 three-class classification problems existed. Classification was conducted by means of five-fold
201 cross-validated naïve Bayes classifier. The chosen classifier utilizes the total probability
202 theorem and the Bayes theorem to estimate the posterior probability (i.e., the probability that
203 the features of an observation belong to a particular class) for each class. Then, for each

204 observation, corresponding posterior probabilities are compared to each other and the most will
205 be selected as the outcome of the classification. Naïve Bayes classifier performs classification
206 on the assumption that features of each class have statistical independence, whereas sometimes
207 this is not the case. This classifier, however, works well in practice (Hastie et al., 2009).
208 Posterior probability was calculated as follows:

209

$$\hat{P}(k|X_1, \dots, X_p) = \frac{\pi(k) \prod_{j=1}^p P(X_j|k)}{\sum_{k=1}^M \pi(k) \prod_{j=1}^p P(X_j|k)} \quad (5)$$

210

211 Where, k is the class index, X_1, \dots, X_p are the features for each observation, and $\pi(k)$ is the
212 empirical prior probability of class k . It is worth mentioning that the hyperparameters of the
213 naïve Bayes classifier for each training fold was determined by Bayesian optimization.

214 In order to evaluate the amount of classification performance, classification accuracy and
215 Cohen's kappa value were computed. Classification accuracy was defined to be the number of
216 correctly classified observations divided by the number of classified observations. According
217 to (Billinger et al., 2012), Cohen's kappa value was calculated as follows:

218

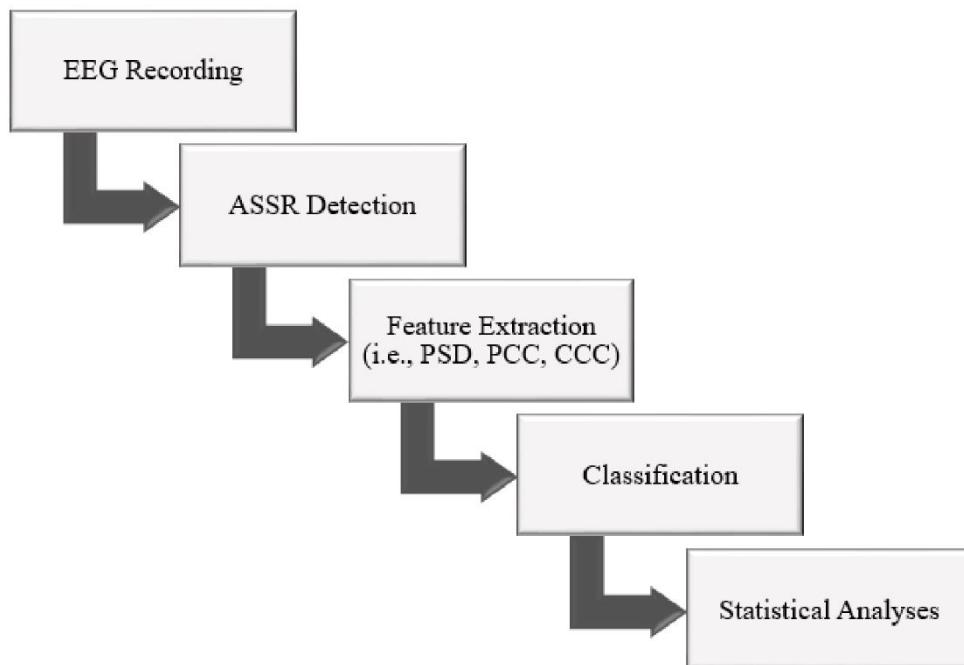
$$p_e = \frac{\sum_{i=1}^M C_{i,:} C_{:,i}}{N^2} \quad (6)$$

$$\kappa = \frac{Acc - p_e}{1 - p_e} \quad (7)$$

219

220 Where, p_e is the chance level, $C_{i,:}$ is the i -th row of confusion matrix, $C_{:,i}$ is the i -th column of
221 confusion matrix, M represents the number of classes, and N is the total number of classified
222 observations. Besides, κ and Acc are the Cohen's kappa value and the classification accuracy,
223 respectively.

224 **Experimental Design and Statistical Analysis.** In order to examine the effect of stimuli type
225 (i.e., simple, rhythmic) and feature (i.e., PSD, PCC, CCC) on the classification performances,
226 we used the classification performance measures (i.e., accuracy, Cohen's kappa value) for all
227 the subjects (12 female, 7 male) as the dependent variable. Features and stimuli types were the
228 within-subjects factors. All these were carried out via within-subjects repeated measures
229



230
231 **Figure 3.** Signal recording and analyses procedure.
232
233 ANOVA. Mauchly's test checked whether the sphericity assumption held. Further,
234 Greenhouse-Geisser approximation corrected the degrees of freedom. We selected Tukey's
235 honest significant difference to perform *post hoc* comparisons.
236 In addition, Wilcoxon signed rank test was used to see whether the level of stimuli-induced
237 fatigue corresponding to the two sets of stimuli differ significantly within the subjects. In this

238 statistical design, subjects` fatigue was the dependent variable and type of the stimuli sets (i.e.,
239 simple and rhythmic) were within-subjects factors.

240 To investigate whether there is a relationship between psychological factors, which were
241 evaluated via the questionnaires, and the reported fatigue, Spearman`s correlation test was
242 performed. All the analyses were conducted in MATLAB R2016b (MathWorks Inc., Natick,
243 MA, USA).

244 Moreover, signal recording and analyses procedure is illustrated in **Figure 3**.

245

246 **Results**

247 **Response detection**

248 For each stimulus, amplitude spectrum of its corresponding EEG was computed. We checked
249 whether the amplitude spectrum at f_m was larger than the mean+3×standard deviation (SD) of
250 the amplitude spectrum at frequencies in the range of (f_m-1 to f_m-5) and (f_m+1 to f_m+5) (Tanaka
251 et al., 2015) to make sure that ASSR was appeared. For simple and rhythmic stimuli set,
252 amplitude spectrum corresponding to one stimulus is denoted in **Figure 4**. as a representative,
253 because all the ASSRs satisfied the aforementioned condition (Tanaka et al., 2015).
254 Consequently, these newly designed auditory stimuli with multiple message frequency coding
255 elicited robust ASSRs.

256

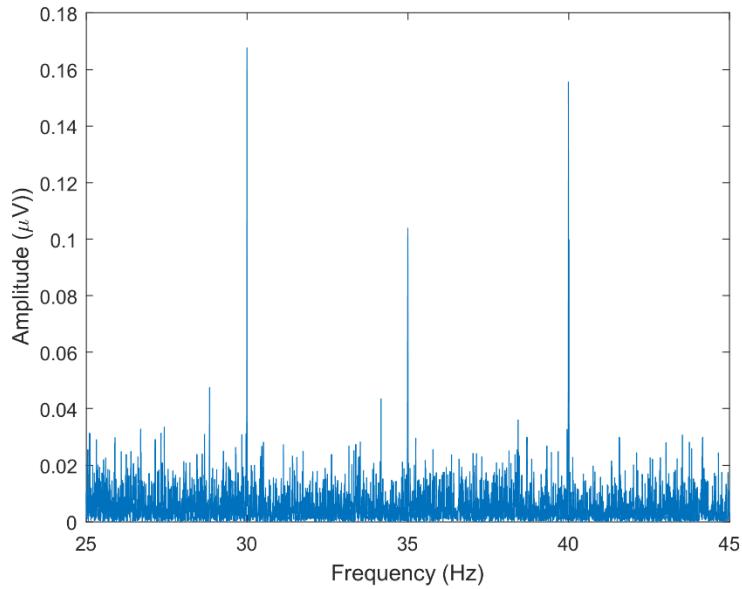
257 **Behavioral results**

258 After listening to each stimulus, participants reported the amount of fatigue that they
259 experienced by listening to that stimulus. All the subjects reported their level of fatigue as an
260 integer number in the range from 0 (minimum) to 10 (maximum) according VAS. In
261 comparison to the simple stimuli, the rhythmic stimuli caused significantly lower fatigue ($p =$
262 0.005, Wilcoxon signed rank,). This confirms our second hypothesis (fatigue reduction using

263

264

A



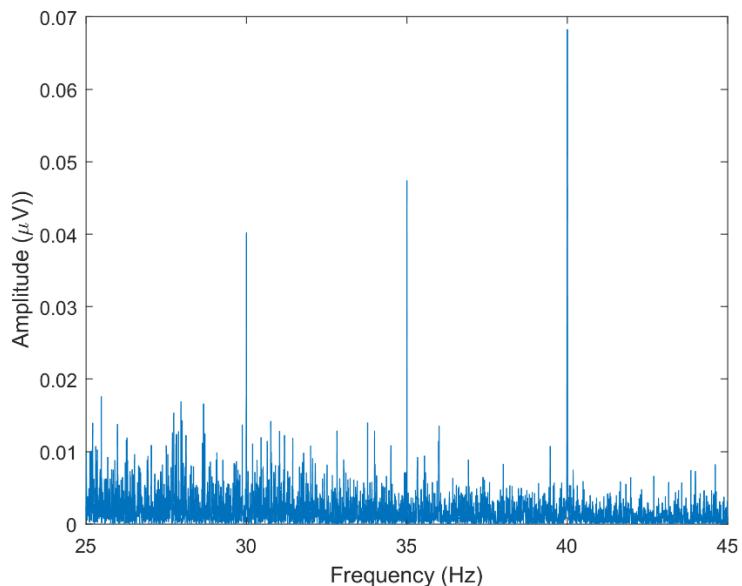
265

266

267

268

B



269

270

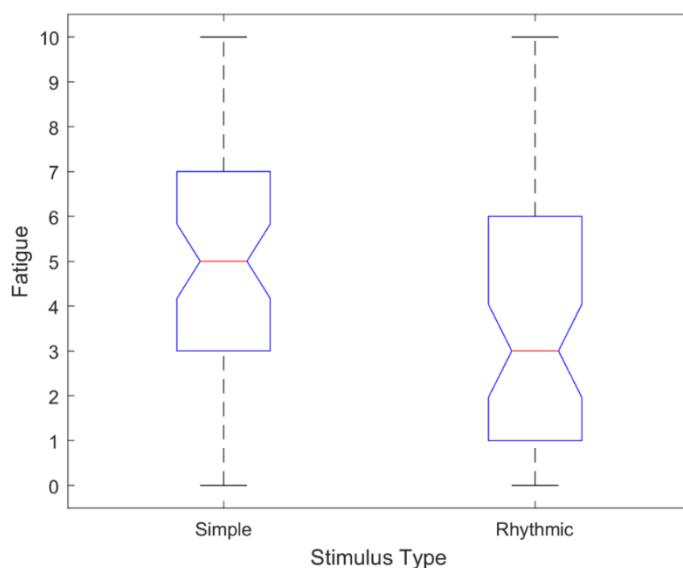
271

Figure 4. Amplitude spectrum of the responses to **A**, simple set. **B**, rhythmic set.

272

273 the proposed novel rhythmic stimuli set). Boxplot representation of fatigue due to the stimuli
274 in each set is illustrated in **Figure 5**. In addition, there was not any significant correlation
275 between psychological factors and fatigue caused by listening to each stimulus. This is an
276 indication of the fact that the subjects truly reported the fatigues that were chiefly caused by
277 listening to the stimuli, regardless of their psychological factors. For each stimulus, scatter plot
278 of the data that yielded strongest Spearman's correlation coefficient, along with the best
279 monotone curve fitted to the data are denoted on **Figure 6**. In each case, the best-fit curve was
280 obtained through nonlinear least squares method. Details of all the Spearman tests (Spearman's
281 correlation coefficients and corresponding *p*-values) are illustrated **Table 2**.

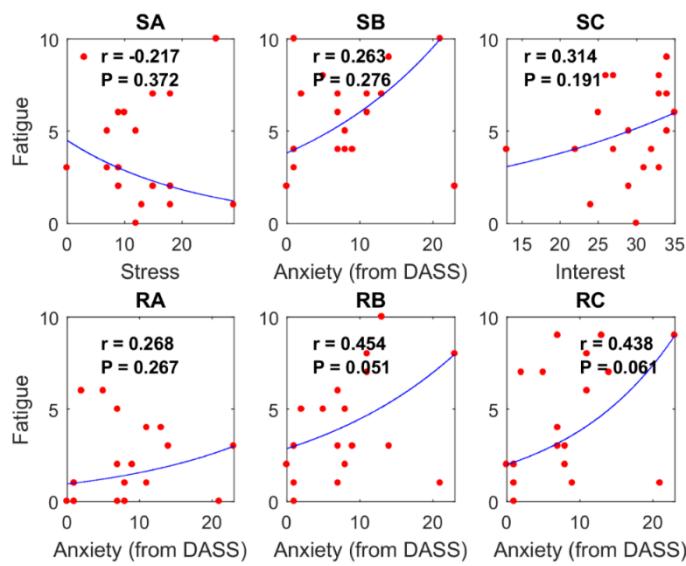
282



283

284 **Figure 5.** Boxplot representation of fatigue caused by the stimuli (fatigue levels were integers from 0 (minimum
285 fatigue) to 10 (maximum fatigue) according to VAS). Rhythmic set significantly reduced the subjects' fatigue (*p*
286 = 0.005, Wilcoxon signed rank).

287



288

289 **Figure 6.** Scatter plots of the data that yielded strongest Spearman's correlation coefficient between the
290 psychological factors and fatigue caused by each stimulus (each plot's name), along with the best monotone curve
291 fitted to the data. There was not any significant correlation between psychological factors and fatigue caused by
292 listening to each stimulus. In each plot, r represents Spearman's correlation coefficient, while P is the p obtained
293 in the Spearman's correlation test.

294

295 **Classification performance**

296 To investigate whether the designed stimuli yield intrinsically discriminative responses, we
297 performed classification (for features and classifier parameters used, see Materials and
298 Methods). For both sets of stimuli, high classification accuracy and Cohen's kappa value (up
299 to a maximum of 100% and 1, respectively) were obtained. There was no significant difference
300 between the responses to the simple and rhythmic stimuli sets in terms of classification
301 performance ($F(1,15) = 4.06$, $p = 0.062$, repeated measures ANOVA). Furthermore, there was
302 not any significant difference between PSD, PCC, and CCC features in terms of classification
303 performance ($F(2,30) = 1.21$, $p = 0.307$, repeated measures ANOVA). These indicate that the
304 responses to the stimuli in each set are sufficiently discriminative. Further, the results show
305 that all the extracted features were discriminant measures for the responses to each set. Group
306

307 **Table 2. Spearman's correlation test (r: Spearman's correlation coefficient, P: p obtained via the test).**

308 **There was not any significant correlation between the psychological factors and stimuli-caused fatigue**

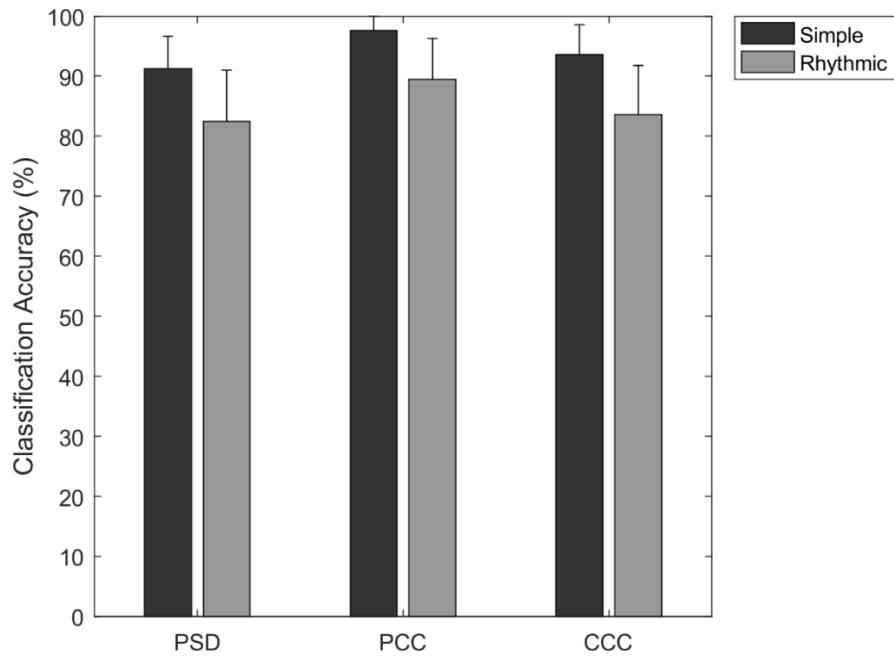
Challenge	Interest	Success	Anxiety	Anxiety		Stress		
		Probability	(QCM)	Depression	(DASS)			
		r = -0.088	r = -0.055	r = 0.099	r = 0.086	r = -0.122	r = -0.098	r = -0.217
Fatigue Caused by SA		P = 0.721	P = 0.823	P = 0.685	P = 0.726	P = 0.619	P = 0.691	P = 0.372
		r = 0.049	r = 0.185	r = 0.086	r = 0.114	r = 0.025	r = 0.263	r = 0.015
Fatigue Caused by SB		P = 0.843	P = 0.449	P = 0.726	P = 0.643	P = 0.920	P = 0.276	P = 0.952
		r = 0.149	r = 0.314	r = 0.109	r = 0.084	r = -0.127	r = 0.176	r = -0.101
Fatigue Caused by SC		P = 0.543	P = 0.191	P = 0.658	P = 0.736	P = 0.603	P = 0.470	P = 0.680
		r = -0.074	r = -0.160	r = -0.055	r = 0.015	r = 0.071	r = 0.268	r = -0.006
Fatigue Caused by RA		P = 0.765	P = 0.512	P = 0.823	P = 0.951	P = 0.772	P = 0.267	P = 0.981
		r = -0.012	r = -0.190	r = -0.047	r = 0.170	r = 0.371	r = 0.454	r = 0.308
Fatigue Caused by RB		P = 0.962	P = 0.435	P = 0.848	P = 0.488	P = 0.118	P = 0.051	P = 0.200
		r = 0.176	r = -0.070	r = -0.298	r = 0.049	r = 0.247	r = 0.438	r = 0.413
Fatigue Caused by RC		P = 0.472	P = 0.776	P = 0.216	P = 0.844	P = 0.308	P = 0.061	P = 0.079

309

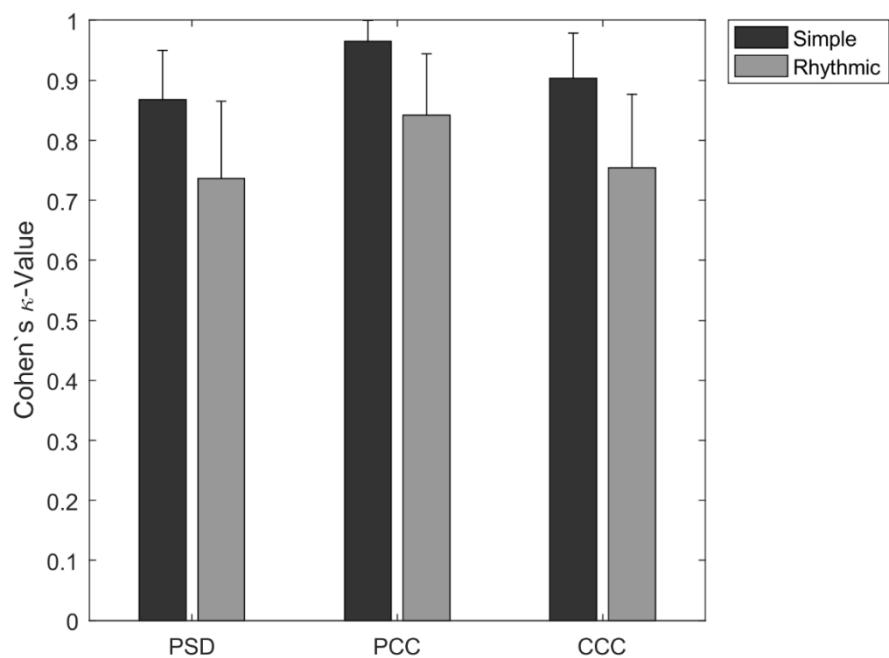
310 **Table 3. Between-subjects classification performance for different stimuli sets and features**

	PSD		PCC		CCC	
	Simple	Rhythmic	Simple	Rhythmic	Simple	Rhythmic
Accuracy (%)	92.98	88.89	93.57	81.29	94.15	83.04
Cohen's kappa value	0.90	0.83	0.90	0.72	0.91	0.75

311



312



313

314 **Figure 7. Top**, Group means of the classification accuracy for the three features (PSD, PCC, CCC) as a function
315 of stimuli type (illustrated as Simple, Rhythmic). **Bottom**, Group means of the Cohen's kappa value for the three
316 features (PSD, PCC, CCC) as a function of stimuli type (illustrated as Simple, Rhythmic).

317

318 **Table 4. A comparison between the results of this paper and those of some relevant ASSR studies**

Study	Subjects	Number of stimuli / Type	Segment (seconds)	Average classification accuracy (%)	Fatigue measurement
(Kim et al., 2011)	6 normal	2 / single-message AM tones	20	76.25	Not included
(Nakamura et al., 2013)	8 normal	2 / single-message AM speech sentence	9	78.6	Not included
(Kaongoen and Jo, 2017)	10 normal	2 / simple single-message AM tones	21	82.90	Not included
(Heo et al., 2017)	6 normal	2 / simple single-message AM tones	20	74	Not included
(Heo et al., 2017)	6 normal	2 / single-message AM natural sound carrier	20	87.67	Not included
(Heo et al., 2017)	6 normal	2 / single-message AM musical carrier	20	89.67	Not included
(Shamsi et al., 2017)	19 normal	3 / simple single-message sinusoidal AM tone	20	82.46	Median: 4
(Shamsi et al., 2017)	19 normal	3 / rhythmic single-message sinusoidal AM sequence	20	80.70	Median: 2
This work	19 normal	3 / simple multiple-message sinusoidal AM tone	20	PSD: 91.23 PCC: 97.66 CCC: 93.57	Median: 5
This work	19 normal	3 / rhythmic multiple-message sinusoidal AM sequence	20	PSD: 82.46 PCC: 89.48 CCC: 83.63	Median: 3

320 means of the classification accuracy and Cohen`s kappa value for different conditions (i.e.,
321 features) as a function of the stimuli type (i.e., simple, rhythmic) are illustrated in **Figure 7**.
322 The results show that all the average classification accuracies are well above 70%, which is the
323 minimum acceptable classification accuracy in BCI systems. Thus, the responses to the stimuli in each
324 set are highly discriminative. In other words, our first hypothesis was confirmed. To investigate
325 whether there is generalizability in terms of response discrimination, we performed between-
326 subjects classification for the responses to each set. Classification accuracy and Cohen`s kappa
327 value for between-subjects classification according to each feature are listed in **Table 3**.

328

329 **Discussion**

330 According to the facts that humans enjoy listening to rhythmic sounds (Zhou et al., 2016; Heo
331 et al., 2017) and rhythmic stimulation influences the intrinsic neural oscillatory characteristics
332 (Herrmann et al., 2016), it seems that utilizing rhythmic auditory stimuli in the experiments
333 that aim to evoke and examine auditory responses in the brain reduces the subjects` fatigue.
334 Thus, this study was carried out to test our two hypotheses 1) the ASSRs to the novel stimuli
335 with multiple message frequency coding are highly discriminative, and 2) listening to the novel
336 rhythmic stimuli set with multiple message frequency coding reduces the subjects` fatigue. All
337 these were conducted to determine whether the stimuli introduced in this paper have enough
338 feasibility (in terms of classification performance and subjects` fatigue) to be used in an aBCI.
339 In some previous studies, rhythmic sinusoidal amplitude-modulated tones were used to elicit
340 EEG (Heo et al., 2017; Shamsi et al., 2017) and MEG (Kuriki et al., 2013), but all of them
341 utilized single message frequency. Further, response classification and subjects` fatigue
342 evaluation were not conducted in (Kuriki et al., 2013). Although user acceptance evaluated in
343 (Heo et al., 2017), user fatigue was not taken into account. Thus, both the stimuli sets designed
344 in this study were novel in the sense of having multiple message frequency coding. In addition,

345 response classification and fatigue evaluation were carried out for these stimuli for the very
346 first time. For a better insight into the novelty of this work, a comparison between the results
347 of this paper and those of some relevant ASSR studies, which performed response
348 classification, are illustrated in **Table 4**.

349 Robust peak in ASSR spectrum at message frequencies (corresponding to the envelope of
350 the stimuli) is consistent with previous findings (Lopez et al., 2009; Kim et al., 2011;
351 Nozaradan et al., 2012; Kuriki et al., 2013; Kaongoen and Jo, 2017) and confirms the notion
352 that human's auditory system acts like an envelope detector, which can be an amplitude
353 demodulator (Miyazaki et al., 2013). In addition, amplitudes of the responses to the rhythmic
354 set were lower than those of the simple set. This may be due to the more complex structure of
355 the rhythmic set, compared to that of the simple set. There is relevant supporting evidence that
356 more complex stimuli elicited less amplitude, when compared to stimuli with simpler structure
357 (Nakamura et al., 2013; Shamsi et al., 2017).

358 Moreover, the rhythmic stimuli set resulted in less fatigue in the subjects, compared to that
359 of the simple stimuli set. This is in agreement with the findings in our previous study on the
360 comparison between the fatigue levels that simple and rhythmic single-message sinusoidal AM
361 stimuli can cause (Shamsi et al., 2017) and confirms our second hypothesis. In addition, the
362 insignificant and infinitesimal correlation between the fatigue and the psychological factors
363 can ensure us that the subjects truly reported the fatigue that was chiefly caused by listening to
364 the stimuli, regardless of their psychological factors.

365 We were able to perform highly accurate, precise and reliable classification on within- and
366 between-subjects responses without any artifact rejection. This shows that there was adequate
367 inherent discrimination even at the raw signal level for the responses to each stimuli set. It can
368 be seen from the within-subjects classification performance results that: 1) stimuli with
369 multiple message frequencies generate highly distinguishing ASSRs, so they have the potential

370 be utilized in aBCI to increase the number of available commands, and therefore the
371 information transfer rate, by means of multiple permutations of just a few message frequencies,
372 which is accessible via the coding presented in this paper. In other words, fewer message
373 frequencies (N in the proposed multiple message coding, compared to N^N in single-message
374 SAM tones) can generate N^N commands in aBCI, 2) the rhythmic stimuli elicit discriminative
375 responses, which are as distinct as that of the simple stimuli, 3) all the features (PSD, PCC, and
376 CCC) are discriminant measures for the classification of the ASSR to the stimuli with multiple
377 message frequencies. Also, high amounts of between-subjects classification performance
378 indicates that the ASSRs to the stimuli in each set were reliably distinct and generalizable.
379 Furthermore, all the average classification accuracies were far above 70%, which is sufficient
380 for a BCI system. In other words, our first hypothesis was confirmed. Thus, the stimuli
381 designed in this paper have the adequate potential to be corresponding to several different
382 commands and generate distinct responses in BCI systems.

383 The average classification performances obtained in this study outperformed previous
384 studies, which utilized single-message AM tones (Lopez et al., 2009; Kim et al., 2011; Heo et
385 al., 2017; Kaongoen and Jo, 2017; Shamsi et al., 2017) and single-message AM sentences
386 (Nakamura et al., 2013). Particularly, the average classification performances obtained for our
387 simple set was higher than those of a research, which used single-message AM natural sound
388 carriers (Heo et al., 2017). However, the average classification performances for our rhythmic
389 set was a bit lower than those of a study, which made use of single-message AM instrumental
390 music carriers (Heo et al., 2017). It is worth mentioning that in the current study, each stimulus
391 was presented separately, while the stimuli in most of the compared studies were played
392 simultaneously, which may decrease their classification performance. In other words, for each
393 subject of the current study, each stimulus played, the fatigue reported by the subject was
394 written down, and another stimulus was presented, and so on. There were two reasons for this:

395 1) we wanted to ensure that whether the stimuli in each introduced set evoke adequate
396 inherently distinguishable responses in the brain, 2) we wanted to measure the amount of
397 fatigue that each stimulus caused to each subject, so we had to present the stimuli separately
398 (i.e., one by one). Although simultaneous presentation of the stimuli is required in BCI
399 paradigms, this is not the case in our study, which is not a BCI paradigm. This study is a
400 preliminary step that investigated the feasibility of utilizing the proposed stimuli in aBCI
401 paradigm. For this purpose, the amount of inherent distinguishability between the responses in
402 each set, along with subjects` fatigue were measured through the separate presentation.
403 Therefore, our purpose required this kind of stimuli presentation. However, in simultaneous
404 presentation of the stimuli, f_c coding in the rhythmic set will help the users to focus on and
405 discriminate between the stimuli. This implies that the classification performance of the
406 responses in the simultaneous stimuli presentation would not be too different from our results,
407 which are obtained via separate stimuli presentation.

408 The results showed that stimuli in each set have sufficient inherent discrimination to the
409 extent that it is worthwhile to use these novel auditory stimuli with multiple message frequency
410 coding in a BCI experiment. If we are asked to choose one of our proposed stimuli sets to be
411 utilized in BCI studies, the choice will be the “rhythmic set”. The reason is listening to the
412 rhythmic set reduced the subjects` fatigue and the brain responses to the rhythmic set were
413 classified via a common classifier, with a high performance close to the simple set, so this set
414 will be able to increase the number of possible commands by permutation of the message
415 frequencies of its stimuli.

416 Sinusoidal amplitude-modulated tones are helpful in studies concerning encoding of
417 envelope and periodicity in human`s auditory system. Moreover, they can be used in ASSR-
418 based BCI systems. Therefore, exploring sinusoidal AM tone-evoked ASSR is chiefly
419 important. In this paper, each stimuli set contained ascending, descending and one of the

420 possible zigzagging codings of message/carrier frequency. For future work, it is suggested to
421 explore ASSR to other possible zigzagging permutations of message/carrier frequency, and
422 make a comparison between the responses to stimuli with different coding types (ascending,
423 descending and zigzagging) and frequency effects. Also, testing auditory stimuli constructed
424 with other modulations (e.g., frequency modulation (FM), pulse width modulation (PWM),
425 etc.) would be valuable. Further, conducting the experiment performed in this paper on
426 completely locked-in state syndrome (CLIS) patients is proposed for future work to see whether
427 they are useful for those individuals. In this study, we aimed at exploring the responses in
428 common domains (e.g., time and frequency). However, nonlinear and/or time-frequency
429 analyses can be performed and compared in future studies.

430

431 **References**

432 Billinger M, Daly I, Kaiser V, Jin J, Allison BZ, Müller-Putz GR, Brunner C (2012) Is it
433 significant? Guidelines for reporting BCI performance. In: Towards Practical Brain-
434 Computer Interfaces, pp 333-354: Springer.

435 Drake C, Botte M-C (1993) Tempo sensitivity in auditory sequences: Evidence for a multiple-
436 look model. *Attention, Perception, & Psychophysics* 54:277-286.

437 Furdea A, Halder S, Krusienski D, Bross D, Nijboer F, Birbaumer N, Kübler A (2009) An
438 auditory oddball (P300) spelling system for brain-computer interfaces.
439 *Psychophysiology* 46:617-625.

440 Halder S, Rea M, Andreoni R, Nijboer F, Hammer E, Kleih S, Birbaumer N, Kübler A (2010)
441 An auditory oddball brain-computer interface for binary choices. *Clinical
442 Neurophysiology* 121:516-523.

443 Hastie T, Tibshirani R, Friedman J (2009) The Elements of Statistical Learning, 2nd Edition:
444 Springer-Verlag New York.

445 Heo J, Baek HJ, Hong S, Chang MH, Lee JS, Park KS (2017) Music and natural sounds in an
446 auditory steady-state response based brain–computer interface to increase user
447 acceptance. *Computers in Biology and Medicine* 84:45-52.

448 Herrmann CS, Murray MM, Ionta S, Hutt A, Lefebvre J (2016) Shaping Intrinsic Neural
449 Oscillations with Periodic Stimulation. *The Journal of Neuroscience* 36:5328-5337.

450 Higashi H, Rutkowski TM, Washizawa Y, Cichocki A, Tanaka T (2011) EEG auditory steady
451 state responses classification for the novel BCI. In: 2011 Annual International
452 Conference of the IEEE Engineering in Medicine and Biology Society, pp 4576-4579.

453 Hill NJ, Lal TN, Bierig K, Birbaumer N, Schölkopf B (2004) An auditory paradigm for brain-
454 computer interfaces. In: Proceedings of the 17th International Conference on Neural
455 Information Processing Systems, pp 569-576. Vancouver, British Columbia, Canada:
456 MIT Press.

457 Hoffmann U, Vesin J-M, Ebrahimi T, Diserens K (2008) An efficient P300-based brain-
458 computer interface for disabled subjects. *Journal of Neuroscience Methods* 167:115-
459 125.

460 Höhne J, Schreuder M, Blankertz B, Tangermann M (2011) A Novel 9-Class Auditory ERP
461 Paradigm Driving a Predictive Text Entry System. *Frontiers in Neuroscience* 5:99.

462 Kanoh Si, Miyamoto K-i, Yoshinobu T (2008) A brain-computer interface (BCI) system based
463 on auditory stream segregation. In: Engineering in Medicine and Biology Society,
464 2008. EMBS 2008. 30th Annual International Conference of the IEEE, pp 642-645:
465 IEEE.

466 Kaongoen N, Jo S (2017) A novel hybrid auditory BCI paradigm combining ASSR and P300.
467 *Journal of Neuroscience Methods* 279:44-51.

468 Käthner I, Ruf CA, Pasqualotto E, Braun C, Birbaumer N, Halder S (2013) A portable auditory
469 P300 brain–computer interface with directional cues. *Clinical Neurophysiology*
470 124:327-338.

471 Kaufmann T, Holz EM, Kübler A (2013) Comparison of tactile, auditory, and visual modality
472 for brain-computer interface use: a case study with a patient in the locked-in state.
473 *Frontiers in Neuroscience* 7:129.

474 Kayashima Y, Yamamoto K, Makinodan M, Nakanishi Y, Wanaka A, Kishimoto T (2017)
475 Effects of Canon chord progression on brain activity and motivation are dependent on
476 subjective feelings, not the chord progression per se. *Neuropsychiatric Disease and*
477 *Treatment* 13:1499-1508.

478 Kim D-W, Lee J-C, Park Y-M, Kim I-Y, Im C-H (2012) Auditory brain-computer interfaces
479 (BCIs) and their practical applications. *Biomedical Engineering Letters* 2:13-17.

480 Kim D-W, Hwang H-J, Lim J-H, Lee Y-H, Jung K-Y, Im C-H (2011) Classification of selective
481 attention to auditory stimuli: toward vision-free brain–computer interfacing. *Journal of*
482 *neuroscience methods* 197:180-185.

483 Kleih SC, Herweg A, Kaufmann T, Staiger-Sälzer P, Gerstner N, Kübler A (2015) The WIN-
484 speller: a new intuitive auditory brain-computer interface spelling application. *Frontiers*
485 *in Neuroscience* 9:346.

486 Klobassa DS, Vaughan T, Brunner P, Schwartz N, Wolpaw J, Neuper C, Sellers E (2009)
487 Toward a high-throughput auditory P300-based brain–computer interface. *Clinical*
488 *Neurophysiology* 120:1252-1261.

489 Kübler A, Furdea A, Halder S, Hammer EM, Nijboer F, Kotchoubey B (2009) A brain–
490 computer interface controlled auditory event-related potential (P300) spelling system
491 for locked-in patients. *Annals of the New York Academy of Sciences* 1157:90-100.

492 Kuriki S, Kobayashi Y, Kobayashi T, Tanaka K, Uchikawa Y (2013) Steady-state MEG
493 responses elicited by a sequence of amplitude-modulated short tones of different carrier
494 frequencies. *Hearing Research* 296:25-35.

495 Lopez-Gordo MA, Pelayo F, Prieto A, Fernandez E (2012) An Auditory Brain-Computer
496 Interface with Accuracy Prediction. *International Journal of Neural Systems*
497 22:1250009.

498 Lopez M-A, Pomares H, Pelayo F, Urquiza J, Perez J (2009) Evidences of cognitive effects
499 over auditory steady-state responses by means of artificial neural networks and its use
500 in brain-computer interfaces. *Neurocomputing* 72:3617-3623.

501 Lovibond SH, Lovibond PF (1995) Manual for the depression anxiety stress scales. Sydney,
502 N.S.W.: Psychology Foundation of Australia.

503 Miyazaki T, Thompson J, Fujioka T, Ross B (2013) Sound envelope encoding in the auditory
504 cortex revealed by neuromagnetic responses in the theta to gamma frequency bands.
505 *Brain Research* 1506:64-75.

506 Nakamura T, Namba H, Matsumoto T (2013) Classification of auditory steady-state responses
507 to speech data. In: 2013 6th International IEEE/EMBS Conference on Neural
508 Engineering (NER), pp 1025-1028.

509 Nijboer F, Furdea A, Gunst I, Mellinger J, McFarland DJ, Birbaumer N, Kübler A (2008) An
510 auditory brain-computer interface (BCI). *Journal of Neuroscience Methods* 167:43-50.

511 Nozaradan S, Peretz I, Mouraux A (2012) Selective neuronal entrainment to the beat and meter
512 embedded in a musical rhythm. *Journal of Neuroscience* 32:17572-17581.

513 Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory.
514 *Neuropsychologia* 9:97-113.

539 Tanaka K, Kuriki S, Nemoto I, Uchikawa Y (2013) Auditory Steady-State Responses in
540 Magnetoencephalogram and Electroencephalogram: Phenomena, Mechanisms, and
541 Applications. *Advanced Biomedical Engineering* 2:55-62.

542 Vollmeyer R, Rheinberg F (2006) Motivational effects on self-regulated learning with different
543 tasks. *Educational Psychology Review* 18:239-253.

544 Wang T, Deng J, He B (2004) Classifying EEG-based motor imagery tasks by means of time–
545 frequency synthesized spatial patterns. *Clinical Neurophysiology* 115:2744-2753.

546 Wolpaw JR, Birbaumer N, McFarland DJ, Pfurtscheller G, Vaughan TM (2002) Brain–
547 computer interfaces for communication and control. *Clinical Neurophysiology*
548 113:767-791.

549 Zhou S, Allison BZ, Kübler A, Cichocki A, Wang X, Jin J (2016) Effects of Background Music
550 on Objective and Subjective Performance Measures in an Auditory BCI. *Frontiers in*
551 *Computational Neuroscience* 10:105.

552