Research Article

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Cortical alpha oscillation during 3 khz steady-state sinusoidal electric current stimulation

Abstract

Little is known about the changes in ongoingcortical rhythms due to application of the steady-state sinusoidal electrical stimuli of 3 kHz, although it has been shown to elicit tactile sensations. In addition, it is known that somatosensory stimulation attenuates ongoing alpha rhythm in centroparietal cortex. Thus, the present work aimed to evaluate alpha rhythm alterations in sensorimotor area and sensations perceived with application of 3 kHz sinusoidal stimulus. Sensory perception threshold (ST) was measured in ten healthy volunteers for posterior stimulation in three distinct stimulus intensities (1.1xST, 2xST and 3xST). Cognitive evaluation of perceived sensations was obtained through questionnaires and cortical alpha rhythm blockade profile was evaluated through the classical event-related synchronization/desynchronization method. Results showed alpha attenuation in the central cortex bilaterally, in the ipsilateral pre-frontal cortex and contralateral parietal cortex during stimulation. Moreover, there was a tendency of bilateral centroparietal alpha rhythm desynchronization increase with stimulus intensity. In conclusion, sinusoidal electrical stimulation may be useful for disease diagnostics and treatment as well as neurofeedback for brain-machine interface (BMI) applications. Patients may benefit from the novel objective method proposed for assessment of tactile perception, mainly, who might not have their cognition preserved (e.g., stroke).

Keywords: alpha rhythm desynchronization, sensorimotorintegration, sensory threshold, sinusoidal electrical stimulation

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Introduction

Electrical stimulation has been widely used in clinic and research, especially concerning rehabilitation (i.e., functional electrical stimulation),[1] pain relief (i.e., transcutaneous electrical stimulation) and evaluation of sensory and cognitive aspects in individuals.[1,2] Most of these electrical stimulation techniques make use of pulsatile stimuli, which are also a powerful tool for generating mainly transient somatosensory evoked potentials (SSEPs). In turn, the SSEP is used for both central and peripheral nervous systems' evaluation, enlightening complications in conduction and lesions in somatosensory pathways, thus aiding in the assessment of its locations and guiding for prognosis.[2]

Taking this into account, SSEPs mainly reflect sensory aspects or 'bottom-up' mechanisms (i.e., evoked responses) that associate with forward neuronal projections - although this theoretical framework is currently under debate.[3,4] In contrast, induced responses have been reportedly linked to cognitive demand - such as attention and perception[3] - and its role has been interpreted as 'top-down' modulation through lateral or backward connections. Evaluation of induced responses to somatosensory stimuli may be of great importance for evaluating stroke patients' cognition and objectively assessing treatment improvements, especially considering the impaired cognition and sensory dysfunction facet commonly associated with the condition.

Among the sensory modalities, the tactile sense is greatly impaired in stroke patients.[5] Somatosensory tactile input from the environment (i.e., texture, pressure, size, shape) activates mechanoreceptors present in the skin, which are associated with thick myelinated Aβ-fibers.[6]

To assess neuronal responses related with Aβ-fibers' activation, many physiological stimuli have been used, such as vibratory stimuli[7] or actual objects (e.g., brush strokes).[8] Electric pulse stimulus has also

been extensively used with this purpose, [9] and although it has been reported that it seems to evoke tactile perception artificially in a given intensity,[9] it is known that it provides recruitment of thick fibers firstly (Aβ) and thin fibers in a second moment (Aδ and C), especially with increasing stimulus intensities.[10,11] Selectively activating Aβ-fibers could be rather useful for disease evaluation – i.e., diagnosis and progression of conditions that involve sensorial and tactile loss, such as stroke, diabetes mellitus, phantom limb pain and leprosy.[12-16]

During the past two decades, studies have shown that selectively activating Aβ-fibers ought to be attainable by using sinusoidal electrical stimulation of high frequencies, such as 2 kHz and 3 kHz, at the sensory threshold (ST) level as a psychophysical evaluation [13-17] This is usually assessed through subjective questionnaire answers, where participants have to decide on words from a given list, that describe best the sensations felt after stimulation. Thus, it is a forced-choice paradigm that highly depends on individual's cognitive state, and whether this type of stimuli elicits conscious tactile-related responses cortically was not yet assessed.[9,13,14,16]

Cognitive function can be estimated by analyzing patterns on ongoing brain oscillations in the electroencephalogram (EEG). A decrease (ERD-event-related desynchronization) or increase (ERS-event- related synchronization) in an ongoing cortical rhythm's energy can be used as an objective tool for assessment of sensorimotor tasks.[18] The blocking of alpha rhythm (8-13 Hz) has been associated with event or task-specific aspects and might arise from cortical connectivity between somatosensory and motor cortex with other integrative areas involved in several aspects of motor planning and execution.[19] Thus, somatosensory stimulation affects ongoing centroparietal alpha rhythm in both hemispheres with electrical pulse, vibration [7,20] and actual objects as stimuli.[8,21]

Thus, the present work aims to assess whether the 3 kHz stimulus in fact activates tactile-related structures cortically (alpha ERD/ERS

profiles). We expect that alpha rhythm desynchronization (ERD) would also occur in the centroparietal cortex with the steady-state 3 kHz sinusoidal stimulus. It is also expected that with varying stimulus intensity, there would be an increased or decreased perception of tactile stimuli, which would reflect in a higher or lower suppression of the alpha rhythm. This would indicate the possibility of inferring stimulus intensity from ERD evaluation and thus, it could be a useful parameter for sensory discrimination, cognitive evaluation (i.e., stroke) and brain-machine interface training programs (i.e., as neurofeedback, aiding in motor control in patients).[12]

Methodology

Participants

Ten right-handed adult volunteers with ages varying from 24 to 35 years (mean=27.6, SD=4.2) participated in the present study (five males), with previous informed consent, which was approved by the Ethics Committee for Research, a unified national system (CEP/CONEP; Certificate of Presentation for Ethical Consideration: 44944515.4.0000.5257). Volunteers did not present history of neuropathic disease, damage in peripheral and central nervous systems or made use of medications that could alter their sensorial perception.

Experiments took place in a controlled environment, with temperature stabilised from 23-25ºC. All participants sat comfortably in an upright position starring at the wall; arms supported by the armchair, maintaining forearm pronation and were instructed to remain relaxed and to move as little as possible during EEG signal acquisition.

Experimental design

Study design consisted of two parts: (*i*) measurement of participant's current perception threshold – or sensory threshold (ST) - to 3kHz sinusoidal stimulus, corresponding to the smallest electric current intensity capable of evoking sensory perception; (*ii*) EEG signal acquisition, which consisted of nine blocks of stimulation. All blocks consisted of 20 stimuli each, 5 seconds long, intercalated with 10 seconds without stimulation as a resting period. Blocks varied on stimuli intensities, as follows: The first three contained stimuli of 1.1xST (1.1 times the individual's calculated sensory threshold) each; the middle three blocks, 2xST and the last three, 3xST. Block order was performed in this manner (i.e., with crescent intensities) to avoid sensory accommodation.

ST evaluation

The ST was evaluated through the current source Neurostim equipment.[13,14] Electrodes used for electrical stimulation were gold planar concentric (anode as a rim of 9-7 mm diameter and cathode as a 2 mm disc), suggested to have better specificity for Aβ-fiber stimulation, due to its increased focality and relative deepened electrical current density.[16,22] Stimulation electrode was placed on the dorsum of the right hand, on the anatomical snuffbox, for radial nerve stimulation. Before electrode positioning, the skin under it was cleaned and gently scraped with an alcohol (70%) embedded gauze.

The procedure recommended by Martins et al.[13,14] for 3 kHz-ST determination is as follows: (i) Obtaining a crude ST (in µA) based on a ramp protocol, which is characterized by a fixed 1 second-long linear increment (200 µA) which is continuously added until the participant announces feeling something; (ii) Assessment of the fine ST, which involves setting stimulus duration and resting period (4 seconds each), an initial stimulus amplitude - worth half the value established in the ramp protocol – and an increment - worth one

quarter the crude value. This increment is successively added to the previous stimulus amplitude until a button is pressed, when then the increment is halved. This new increment is decreased from the previous stimulus amplitude and whenever the button is pressed, this procedure repeats. Otherwise, the new increment is added to the previous stimulus amplitude. This process is repeated until the system reaches its resolution (8 µA), preceding a validation period. After validation (i.e., assesses whether participants were feeling the threshold stimuli instead of simply being familiarized with stimulus and interval durations) the fine ST is established.

Once ST is obtained, individual's 1.1xST, 2xST and 3xST are calculated for stimulation on the 9-block paradigm previously described.

EEG signal acquisition

EEG recordings were carried out by using a 16 channel acquisitions system[23] and sampling frequency was set at 8 kHz. EEG derivations were located according to the 10-20 international system using silver/silver chloride electrodes. Skin-electrode contact was performed with water-based electrolytic gel. The reference electrode was positioned at Cz and ground electrode on the forehead, 2 cm from nasion. Derivations used for the analysis were F3, F4, F7 and F8 in the frontal area, C3, C4, Pz, P3 and P4 in centroparietal areas and T5 and T6 in temporal areas. One channel was positioned in the subject's right arm (proximally to the elbow interline) for stimulus synchronization and posterior signal comparisons.

Cognitive evaluation

After each block, participants were inferred about their felt sensation from a list of eight words, presented in a random order. Four of each corresponded to sensations associated with thick myelinated fibers Aβ – pressure (*"pressão"*), contraction (*"contração"*), tingle (*"formigamento"*) and vibration (*"vibração"*). The other four with sensations related to the thin fibers (Aδ e C) – heat (*"calor"*), sting (*"picada"*), pins and needles (*"agulhada"*) and itch (*"coceira"*). They were allowed to a forced choice maximum of three words from the list. Similar methodology was employed in previous studies.[16,24,25] In addition, participants were asked to mark a line indicating stimulation subjective discomfort perceived in a continuous line, whose extremities ranged from "No discomfort at all" to "Extremely uncomfortable". This portion of the cognitive evaluation intended to assess perceived stimulus intensity. Line traces were normalised with maximum in each participant.

Data pre-processing

Raw EEG signal from each derivation was synchronized with each trial's commencement of stimulation, based on the arm signal (used as a trigger). After synchronization, the signal was resampled to 400 Hz (passband filter at 1-100 Hz). Then, it was filtered in the band of interest from 8 to 13 Hz. Subsequently, the signal was segmented in individual trials: 5 seconds pre-stimulus, 5 seconds during stimulation and 5 seconds post-stimulus. Artefact rejection's threshold was 3 standard deviations of a previously selected reference window of 20 seconds of signal considered artefact-free. The entire epoch was excluded if 5% of samples were surpassed.

ERD/ERS analysis: Induced events' ERD/ERS analysis follows the classical methodology postulated by Pfurstcheller & Lopes da Silva.[18] Thus, pre-processed signals' mean is subtracted from each individual trial (i.e. to extract the evoked response), then all trials are squared (i.e. so that an energy estimate is obtained) and averaged (i.e., power estimative). At this point, a reference window lasting one second was

chosen - from -4 to -3 seconds – so that a relative appraisal of power could be achieved. Data pre-processing and ERD/ERS analysis were performed with MATLAB software.

Statistical analysis: Wilcoxon signed-rank test was used to compare mean relative power in the periods during stimulation (PD) and periods without stimulation (PW). Whenever outliers were found, they were excluded from statistical analysis and statistical significance level was α=5%. For cognitive evaluation, the nonparametric Friedman test for dependent samples was used. All statistical analysis was performed using IBM SPSS software.

Responses due to felt sensations in each block were categorized as suggested by Martins et al.,[14] in which blocks that contained words related to both groups (thin and thick fibers) are called BOTH, related to thin fibers THIN, and to thick fibers THICK. Thus, evaluation of perceived sensations – and indirect fiber activation - was performed by each group's percent change due to stimulus intensity increase.

Results

ERD in the alpha-band

Figure 1 illustrates relative power grand average for each derivation at stimulus intensity of 1.1xST. For this intensity, three participants were excluded from analysis due to excessive signal artefact. It was possible to observe by visual inspection a slight ERD at the first seconds of stimulation mainly in C3 (median PD = -8.54%). Without stimulation, the median PW was 2.16% and statistically significant ERD was found ($p = 0.043$). C4 shows trends of ERD ($p = 0.128$). For the other derivations at this intensity, Wilcoxon's p-values were higher than 0.237 (e.g., arm, $p = 0.465$).

Results were similar for the 2xST stimulus intensity (Figure 2), although it is possible to observe an increased amplitude of alpha ERD in derivations C3 (median PD = -19,30%) and C4 (median PD = -9,50%), together with ERD of P3 (median PD = -8,59%) and F4 (median PD = -6,46%). Median PW values were -4,58, -5,98, -2,44 and 0,68 for C3, C4, P3 and F4, respectively. All these derivations showed statistically significant ERD, although for C3 it became more significant ($p = 0.005$) and C4's significance ($p = 0.013$) indicates an increase of ERD accompanied by stimulus intensity increase. The other two p-values were 0.013 and 0.007 for F4 and P3, respectively. *P*-values from the remaining derivations were all above $p = 0.074$ (at P4). At this intensity, three participants were excluded from the arm derivation together with one outlier from F7 for analysis.

It can be also noted a strong ERD during stimulation in C3 (median PD/PW = -20.23/3.91) and C4 (median PD/PW-14.20/0.26) for the 3xST stimulus intensity (Figure 3), although with distinct morphologies: C3's ERD seems to decrease subtly with time, whereas C4's is maintained whilst stimulation is applied. Statistically significant results were observed in F3 ($p = 0.015$), F4 ($p = 0.008$), C3 ($p = 0.005$), P3 ($p = 0.012$), C4 ($p = 0.037$), T5 ($p = 0.028$) and T6 ($p = 0.028$, median PD/PW = -12.17/-4.80). Statistical significance in C3, C4 and F4 (median PD/PW = -8.30/-0,16) were similar to the ones observed at 2xST, suggesting equivalent ERDs in these areas. One outlier was excluded from F3 (median PD/PW = -4.81/2.77), F4 (median PD/PW =-8.81/-1.82) and T5 (median PD/PW = -2.17/2.03) and two outliers were excluded from P3 (median PD/PW = - 18.01/-4.18). Three participants' arm derivations were excludes for analysis. For the remaining derivations, p-values were all higher than 0.074 (e.g., P4, $p = 0.386$).
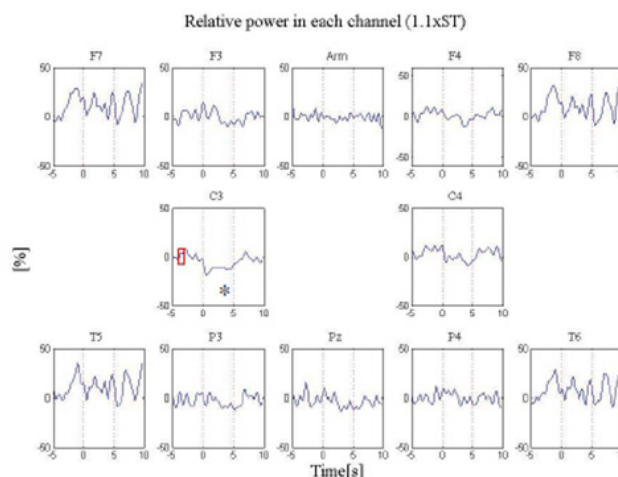

Figure 1 Alpha rhythm's relative power for all participants in each derivation, with 1.1xST stimulus intensity. Reference window for ERS/ERD analysis is outlined in red.
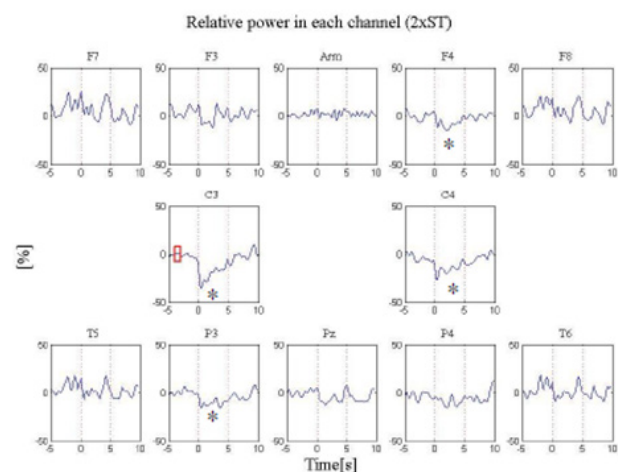

Figure 2 Alpha rhythm's relative power for all participants in each derivation, with 2xST stimulus intensity.
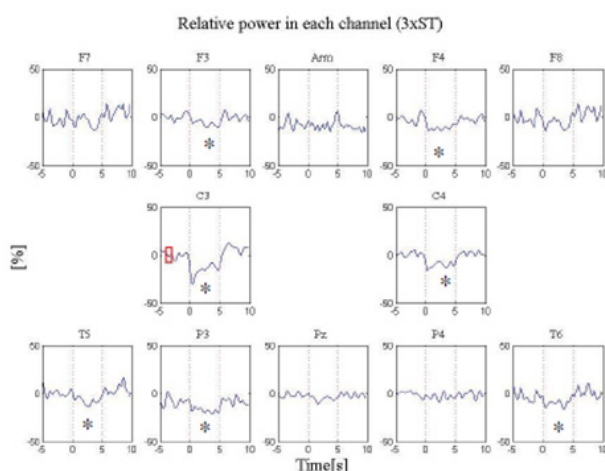

Figure 3 Alpha rhythm's relative power for all participants in each derivation, with 3xST stimulus intensity.

Citation: Volpi LP, Tierra-Criollo CJ. Cortical alpha oscillation during 3 khz steady-state sinusoidal electric current stimulation. *J Neurol Stroke.* 2017;7(1):1–6.
DOI: 10.15406/jnsk.2017.07.00224

Cognitive evaluation

The 1.1xST stimulus intensity proved to be more selective for Aβ (81%) when considering declared perception of sensations (Table 1). In 2xST blocks, participants described 79% of blocks as producing sensations related to the two groups of fibers, whereas in 3xST, this percentage was 71%. In addition, for 1xST and 2xST, 0% of blocks elicited sensations related with thin fiber (Aδ and C) activation, but for 3xST, this percentage was 5%.

Table I Stimuli subjective perception by percent changes through stimulation blocks

Perception	Intensities		
	1.1xST	**2xST**	**3xST**
THICK	81%	21%	24%
THIN	0%	0%	5%
BOTH	19%	79%	71%

The Friedman test showed that subjectively perceived intensity evaluated from the normalized stimulus discomfort scale was statistically significant ($p = 0.001$). Post hoc analysis (Wilcoxon with Bonferroni correction) demonstrated that for all paired intensities there was a significant statistical difference. Median perceived normalized intensity levels for the 1.1xST, 2xST and 3xST trials were 0.054, 0.543 and 0.819, respectively.

Discussion

Results show that with 3 kHz sinusoidal stimuli, there is a significant alpha rhythm desynchronization in the central cortex bilaterally, in the contralateral parietal cortex and in the ipsilateral pre-frontal cortex. It might be possible that with increasing stimulus intensity, there is tendency in increasing alpha rhythm desynchronization in the bilateral sensorimotor cortex, considering the statistical difference increased, although there was no significance statistically (except for C4). It is possible that significance could be seen, for example, with more participants in the experimental design. Conversely, C3 shows a profile in which it becomes less desynchronized as stimulation proceeds, especially after the first second of stimulation, which could imply, for instance, habituation of stimulus.

Cheyne et al.,[8] by using brush strokes stimuli and Nihashi et al.,[26] electrical pulses, observed primary motor cortex alpha-ERD bilaterally and primary somatosensory cortex alpha-ERD contralaterally. In the present work, similar ERD was observed, considering C3 and C4 bilaterally and P3 contralaterally. Thus, it suggests that with sinusoidal electrical stimulus it is possible to elicit tactile sensations which can be objectively evaluated from the EEG signal.

Visually perceived differences in morphology at C3 and C4 could stand for inter-hemispheric communication conveyed through transcallosal pathways and could be an indicative of information flux, from the contralateral central cortex (C3) to the ipsilateral cortex. Nonetheless, future studies would be needed to assess whether this morphological aspect is indeed representative of inter-hemispheric connectivity and information flow. As it concerns stimulus intensity, for 1.1xST there was significant alpha rhythm suppression at C3, although one can notice a trend at C4. It is possible to see this enhancement in suppression for both 2xST and 3xST. Nonetheless, there are no significant changes between activation profiles at centroparietal areas for 2xST and 3xST. Activity in the ipsilateral frontal cortex (F4) for 2xST, bilateral (F3 and F4) for 3xST, and bilateral temporal cortices ERD (T5 and T6) for 3xST, could be explained by higher level cortical processing, involving integration of sensorimotor function regulation as perception and tactile working memory.[27]

Results from the cognitive evaluation confirm that 3 kHz excites preferably Aβ-fibers.[13,14,17] However, it also suggests that with increasing stimulus intensity, participants begin to report words related to thin fibers. This could be either due to recruitment of small-diameter fibers - which is in accordance with has been seen for pulse stimulation[10,11] but not for sinusoidal stimuli[24] - or discomfort perceived due to the higher intensities. In addition, studies with laser stimuli (i.e., used to assess nociceptive conduction) have shown that after stimulation there is a profile of alpha ERS followed by ERD, at the primary somatosensory, parasylvian and medial frontal cortices,[28] which differs from the profile observed in the present study.

Nevertheless, to assess whether the nociceptive system was actually involved, it would be needed to evaluate ERD/ERS patterns due to nociceptive stimulation (i.e., temperature) with further stimuli. Finally, another advantage of the stimulus used in the present study is that its frequency (3 kHz) is out of the EEG range (i.e., typically 0.1-100 Hz), as opposed to many studies using pulsatile stimuli which are usually in this range[9,12] and thus could have lead to deceiving results.

Conclusion

In conclusion, sinusoidal electrical stimulation sensations and cortical rhythm profiles are in accordance with those seen in actual tactile stimulation.[8]

This novel stimulus may substitute other types of tactile stimuli, especially for intensities near the ST. This can be useful for cognitive evaluation and may serve as neurofeedback for distinct therapies and BMI applications.[29] Most notably, patients may benefit from the method proposed for assessment of sensory perception combined with changes in stimulation parameters, such as intensity.

Moreover, this type of stimuli may be considered preferable than pulse stimuli for cognitive evaluation, since assessment for the latter usually involves analyzing discontinuous periods of stimulation, whilst in the present study periods of steady-state stimulation were assessed.

Thus, evaluation of EEG rhythmicity coupled with the 3 kHz sinusoidal stimulus would be an asset for evaluating conditions in which cognition is impaired, such as in stroke patients [5]. Combined with the standard battery of tests currently used to assess cognition improvement (or deterioration) and treatment, this objective technique ought to be a useful tool, especially considering that the most commonly used evaluations highly depend on professionals' experience, leaving space to subjective interpretation.[30]

Acknowledgments

Conflicts of interest

None.

Funding

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