RESEARCH

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Beneficial Effects of Electrostimulation Contingencies on Sustained Attention and Electrocortical Activity

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SUMMARY

Introduction: Chinese acupuncture therapy has been practiced for more than 3000 years. According to neuroimaging studies, electroacupuncture has been demonstrated to be effective via control of the frequency parameter of stimulation, based on the theory of frequency modulation of brain function. **Aims:** To investigate the following: (1) possible sustained effects of acustimulation in improving perceptual sensitivity in attention by comparing before, during, and 5 min following stimulation; (2) relations between commission errors and the motor inhibition event-related potential (ERP) component measured with independent component analysis (ICA); (3) whether habituation would be demonstrated in the sham control group and would be militated by acustimulation in the experimental groups. **Results:** Twenty-seven subjects were divided into three groups (n = 9). d-Prime (d′) derived from signal detection theory was used as an index of perceptual sensitivity in the visual continuous performance attention test. Increased d′ was found during both alternating frequency (AE) and low frequency (LE) stimulation, but with no change in the sham control group (SE). However, only following AE was there a sustained poststimulation effect. Spatial filtration-based independent components (ICs) in the AE group revealed significantly decreased amplitudes of the motor inhibition ICs both during and poststimulation. There was a significant habituation effect from task repetition in the sham group with decreased amplitudes of ICs as follows: the visual comparison component difference between go (correct response) and nogo cues (correct withheld response), the P400 action monitoring and the working memory component in the nogo condition, and the passive auditory component on control trials. **Conclusion:** The results showed associations between acustimulation and improved perceptual sensitivity with sustained improvements following AE, but not LE stimulation. Improvements in commission errors in the AE group were related to the motor inhibition IC. The activational effects of acustimulation apparently attenuated the across-task habituation that characterized the control group.

Introduction

Acupuncture therapy has been practiced in Chinese medicine for more than 3000 years with applications including treating headache, recovering from stroke, and controlling pain [1–4]. Acupuncture can be considered an important complementary medicine practice, with increasing interest from the public, and both the National Institute of Health (USA) and the World Health Organization have summarized guidelines on acupuncture therapy [5,6]. Recent years have seen increased interest in acupuncture therapy in neuroscience including (1) mechanisms of action [7], (2) respondent brain areas [8,9,10], and (3) temporal dynamics such as immediate and/or delayed effects [11,12]. With the increasing development of acustimulation methods for cognition, reliability requirements have become more critical.

Peripheral electrical stimulation may be elicited via electrodes located on the skin (transcutaneous electrical nerve stimulation, [TENS]), and the process is usually named electroacupuncture stimulation or acustimulation [13]. Wang et al. have demonstrated that TENS operates through very similar mechanisms to traditional acupuncture [14], with the mechanism of therapeutic action thought to involve neurotransmitter and opioid peptide systems [1,13–16]. To facilitate the release of neuropeptides in the central nervous system (CNS), the stimulus

parameters of electroacupuncture (intensity, mode, frequency, etc.) can be controlled more precisely than by manual acupuncture. Furthermore, the uncomfortable pain sensation induced by needle manipulation is undesirable and an invasive procedure may also carry the risks of hematoma formation and infection. Electroacupuncture has been the procedure of choice for its comfort, convenience and high repeatability during an individual stimulus program.

Different types of endorphins for analgesia have been selectively released by low- and high-frequency acustimulation [13,17]. Low-frequency stimulation has induced the release of enkephalins, whereas high-frequency stimulation has increased the release of dynorphins in both animal and human experiments [13,18]. Therefore acustimulation in specific frequencies can facilitate the release of specific endogenous opioid peptides for acupuncture-induced analgesia in the CNS. Furthermore, through increases in the level of enkephalins and serotonin in the CNS and plasma acupuncture could affect psychological processes, hence applications for the treatment of depression and anxiety [18–20].

Regarding the temporal effects, both short-term and long-term impact has been examined. It has been proposed that the basic mechanism of the former involves immediate frequency modulation of neuroplasticity [7], and of the latter gene transformation of protein synthesis in specific cortical areas as shown with neuroimaging [8,9]. Dhond et al. have claimed that acupuncture can "enhance the post-stimulation spatial extent of resting brain networks to include anti-nociceptive, memory, and affective brain regions" [11]. It follows from the neuroimaging results, summarized in the Discussion, that there is a likely impact of acustimulation on cognitive functions aside from therapeutic outcome.

There has been limited research showing differential effects between low- versus high-frequency stimulation on cognitive function. With the electroencephalograph (EEG), scalp maps of high- versus low-frequency effects have been investigated in a resting eyes-closed condition, but not in cognitive tasks [12]. In general the relationship between acustimulation and task-evoked brain activity is a neglected area.

As a behavioral task we utilized a continuous performance visual attention test, which has a venerable history in applications in psychopharmacology [21–25] and neurochemistry [26–28]. For about half a century variants of the task have been used to locate impairments and monitor the efficacy of treatments. Applications have ranged from aging [29,30] to sleep deprivation [31], neurobiological disorders including amnesia [32,33], dementia [34], traumatic brain injury [35], and HIV infection [36], and most widely psychopathology including attention deficit hyperactivity disorder (ADHD) [37–39], obsessive compulsive disorder [40,41], depression [42–44], posttraumatic stress disorder [45], and most of all the schizophrenia spectrum [46–52]. The application of signal detection theory [53] to extract a d′ index of sensory sensitivity has been long established in studies of psychopathology [54,55]. This study also uses methods of EEG and event-related potential (ERP) topographic mapping, independent component analysis (ICA), and standardized low-resolution electromagnetic tomography (sLORETA) to study acustimulation and sustained attention.

Our main goals were to investigate the impact of electroacupuncture stimulation on attention and to compare alternating versus low frequencies on behavioral performance, the perceptual sensitivity in attention, topographic EEG, and ERPs for both immediate and poststimulation effects. According to previous research we expected to find that the alternating frequency electroacupuncture was superior to low-frequency stimulation [13,56]. In addition, due to a repeated task design, we hypothesized that habituation would be found in the control group, but not in the two acustimulation groups who would be resistant to habituation because of the activational effects of stimulation. In order to examine if specific cortical areas were affected by electroacupuncture and habituation, we used topographical EEG examination with the ICA method, and applied spatial filtration from a normal database.

Materials and Methods

Subjects

Data were recorded from 30 individuals, but because of technical problems or excessive artifacts, three data sets were excluded from further analysis. Twenty-seven healthy volunteers (20 female, 7 male), mean age = 22.5 (SD = 1.56, range 18–30 years) from Goldsmiths, University of London, participated in the study. Subjects were excluded if they had any history of epilepsy, drug abuse, head injury, or psychiatric disorders. Those participants currently having any sore, pain, cut, skin problems on the hands or receiving psychoactive medication were also screened out. All subjects had not experienced acustimulation before our testing. All had normal hearing and normal (or corrected-to-normal) eyesight. Written consent was obtained prior to the start of the experiment in accordance with the Helsinki Declaration, and the current investigation received the ethical approval from the College Research Ethics Committee.

Participants were randomly assigned to one of three experimental groups of equal size (N = 9) with the method of randomly permuted blocks http://www.randomization.com. Group 1 (alternating frequency, AE) who received stimulation with alternating low (5 Hz) and high (100 Hz) frequencies; Group 2 (low frequency, LE) received stimulation with the low frequency (5 Hz) only; Group 3 (sham electrostimulation, SE) received a control condition with the minimal intensity for electroacupuncture.

Experimental Design

Each subject was asked to perform a continuous performance visual attention task and sat in a comfortable armchair throughout the duration of the experiment in a quiet room. They were seated facing a computer screen, 100 cm in front of them, and were instructed to press a response button whenever a visual target stimulus picture occurred and to withhold responses to other stimuli. Detection accuracy and response time were recorded during the repetitive tasks. All subjects were blind to the stimulation mode and effect. They were told that the machine could stimulate acupuncture points through high-frequency or low-frequency stimulation, and this may or may not give a sensation. Transcutaneous electric acupoint stimulation (Han's acupoint

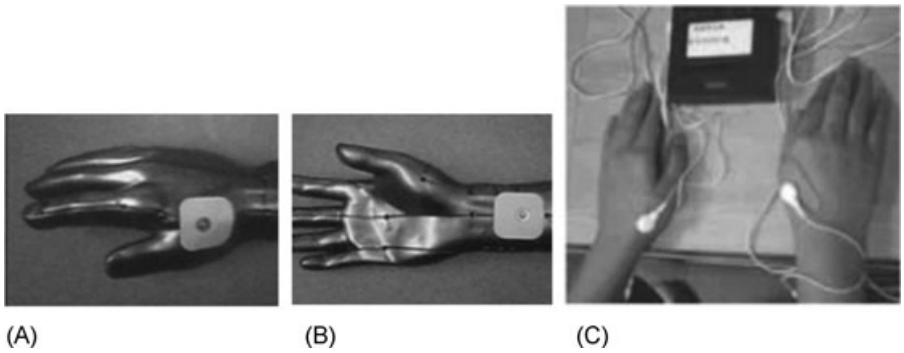

Figure 1 The location of two acupoints. (**A**) HeGu, (**B**) NeiGuan, and (**C**) the application of the stimulator device on both acupoints.

nerve stimulator [HANS], Wearnes Technology, Singapore) was applied. The selected acupoints were LI-4 (HeGu point) and P-6 (NeiGuan point) of both hands. The HeGu point is located at the first inter-interosseous muscle of the hand. The NeiGuan point is located on the anterior surface of the wrist between the tendons of the flexor carpi radialis and the palmaris longus, next to the median nerve, and on average 3–5 cm proximal to the flexor crease. The two acupoints of each hand were stimulated at the same time as a circuit in one output channel of HANS (Figure 1) in order to prevent unusual current overflowing across the body inducing arrhythmia. Subjects received stimulation via four adhesive surface electrodes (size: 4 cm × 5 cm) at the aforementioned bilateral acupoints. The stimulation intensity for the real acustimulation was adjusted to a maximal but comfortable level, slightly below the pain or discomfort threshold, ranging from 7 to 15 mA. For the sham acustimulation the intensity was set at less than 5 mA [57]. Based on the literature review [57–64], we selected sham acustimulation applied to the same points with minimal intensity as our control placebo model, and only the intensity parameter of stimulation was different from the real stimulation groups.

Each subject was instructed to pay no attention to the sensation induced at the stimulated site, and to focus on the attention task. All 27 subjects were assessed by evaluating their behavioral results from the attention task and the event-related EEG measures in the three study stages (before stimulation, during stimulation, and 5 min poststimulation). Each study stage consisted of 5 min eyes closed baseline EEG, 5 min eyes open baseline EEG, and 20 min of the attention task.

Attention Paradigm

The two-stimuli go and nogo task is a subtype of the general go and nogo paradigm. When the "go" stimulus is presented a manual response is required whereas when a "nogo" stimulus is presented the response is to be withheld. The purpose of this design is to examine two types of errors, namely those representing inattentiveness and impulsivity. The task presents stimuli in pairs so that the subject would implicitly be ready to make a decision after the first stimulus in the pair and to respond as fast as possible after the second stimulus is shown on the screen. Here the images were flashed on the screen in pairs within 3 seconds with the instruction to press a button when the target pair occurred. The stimuli were nonlanguage based and consisted of a total of 20 different images of animals (A), plants (P), or humans (H). In addition, each human picture was presented together with a pure tone of 500 Hz of 20 ms duration. Four different categories of trials were shown: "Animal-Animal (A-A)," "Animal-Plant (A-P)," "Plant-Plant (P-P)," and "Plant-Human (P-H)." The duration of the stimuli was 100 ms, and trials were presented in a random order with equal probability. Interstimulus intervals were 1400 ms, and long enough for subjects to prepare their responses; the total interval between trials was 3100 ms. The task consisted of 400 trials, divided into four sessions with 100 trails each, and took around 20 min. The subject had to press a button as fast as possible when the A-A pairs were presented on a screen and ignore other pairs of stimuli (A-P, P-P, P-H, Figure 2) (Psytask user manual, http://www.mitsar-medical.com) [65].

Electroencephalographic (EEG) Recordings and Pretreatment of EEG

Topographical EEG and ERP data of all participants were recorded during the attention task. All neuroelectric data were recorded using the Mitsar 21-channel EEG system, the "Mitsar-201" (CE 0537) manufactured by Mitsar, Ltd. (http://www.mitsar-medical.com), with a 19-channel electrode cap with silver-chloride electrodes that included Fz, Cz, Pz, Fp1/2, F3/4, F7/8, T3/4, T5/6, C3/4, P3/4, O1/2. The cap was placed on the scalp according to the standard 10–20 system (Electro-cap International, Inc. http://www.electro-cap.com/caps.htm). Electrodes were referenced to linked earlobes (off-line) and the input signals were sampled at a rate of 250 Hz (bandpass 0.5–30 Hz). The ground electrode was placed on the forehead. Impedance was kept below 5 kΩ. Electro-oculogram (EOG) data were recorded from electrodes (Fp1/2) placed above the frontal muscles to monitor eye blinking or movements. An EOG correction procedure to remove artifacts was performed and nonspecific artifacts were rejected offline. ERP waveforms were averaged and computed off line and trials with omission and commission errors were automatically

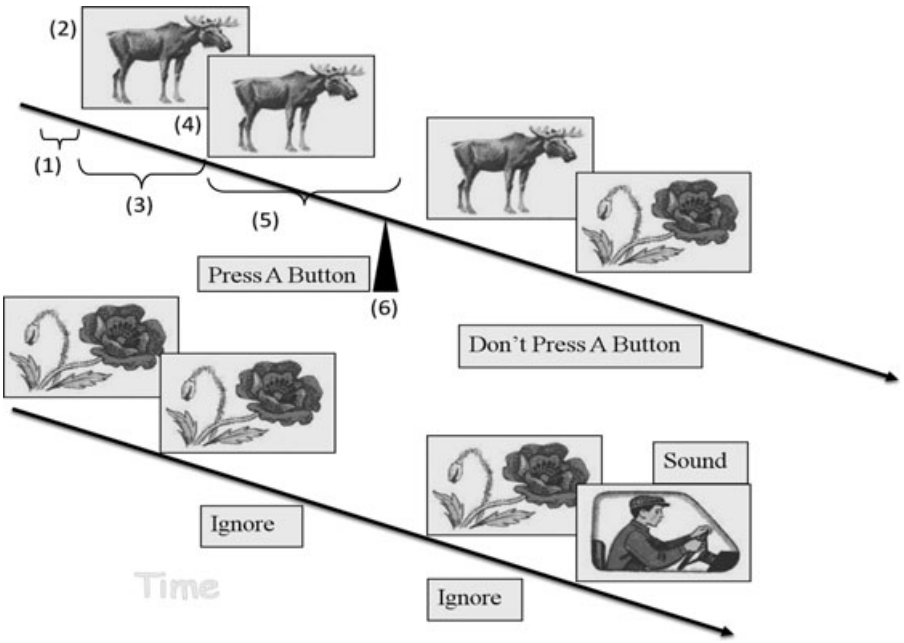

Figure 2 Stimulus presentation in the visual attention task: (1) prestimulus interval, (2) first stimulus, (3) interstimulus interval, (4) second stimulus, (5) poststimulus interval, (6) subject response. Two arrows and lines represent the continuous time axis during the task with four pairs of pictures randomly shown. The first pair, the Animal-Animal (A-A) pair, represents the "go" cue, to which the subject should press the button. The second pair, the Animal-Plant (A-P) pair, represents a "nogo" cue, and the subject should not respond. The remaining two Plant-Plant (P-P) and Plant-Human (P-H) pairs are control condition trials, and the subject should ignore them.

excluded from analysis. All participants performed the attention task three times: before, during, and 5 min poststimulation.

Data management and Statistical Analysis

EEG data analysis was performed using WinEEG 2.83, the commercial software from the Mitsar, Ltd. (http://www.mitsar-medical.com). First, data were digitally filtered using a linear filter to minimize drifts and line noise. ERP data epochs were extracted (0 to 3000 ms) and baseline corrected (−100 to 0 ms). Epochs containing unique, nonstereotyped artifacts (e.g., swallowing, extreme muscle activities with amplitudes over 35 uV, electrode cable movements) were automatically rejected from further analysis, whereas epochs containing repeatedly occurring artifacts (e.g., eye blinks, heart beat artifacts) were corrected using ICA [66,67]. The ICA method [68] (http://sccn.ucsd.edu/eeglab) was implemented in the software, WinEEG, and written by Ponomarev [65]. sLORETA imaging for locating cortical generators provided source computations for the independent components (ICs) using freeware provided by the Key Institute for Brain-Mind Research in Zurich, Switzerland (http://www.uzh.ch/keyinst/loreta.htm) [69].

The behavioral parameters included errors of omission (indicative of inattentiveness), errors of commission (indicative of impulsivity), reaction time (RT) and reaction time variability (RTV). We also introduced the parameter "d-prime" (d′) derived from signal detection theory [53,70]. This takes into account both the ratio of hit rate (H) and the false alarm rate (F) and is used as measure of perceptual sensitivity. Conventionally in calculating d′, H is defined as ("H" = 1-[number of omission errors/number of targets]), and F as ("F" = number of commission errors/number of non-targets). From these formulas, however, the d′ is not simply [H–F], rather, it is the difference between the z-transforms of these two rates and were calculated as [$d' = z(H) - z(F)$]. In other words, d′ measures both of these two error types as an index of perceptual sensitivity [71,72].

To evaluate the effectiveness of acustimulation relative to the sham procedure, a mixed-design ANOVA was used to examine the effects of Group (AE, LE, SE) and Time (before, during, after acustimulation) on behavioral measures. Separate ANOVAs were performed on each of the five measures: omission errors, commission errors, RT and RTV, and d′ with the Bonferroni correction for *post hoc* comparisons. Given the exploratory nature of the study, an uncorrected significance threshold of $P = 0.05$ was used for each of the five ANOVAs in order to preserve a reasonable sensitivity for detecting real effects (i.e., to maintain a reasonable type I error rate). Given this, caution must be used in interpreting each effect, with greater credence given to those effects specifically predicted *a priori*, as outlined in the Introduction. So that the reader can judge which effects would survive a harsher significance criterion, an adjusted alpha of 0.01 was also calculated using a Bonferroni adjustment based on the number of tests (i.e., 0.05/5). The nature of any significant interactions that emerged were explored using

Table 1 Scores (mean ± standard deviations) for attention test measures before, during, and after electrostimulation (3 groups)

Group	go/nogo Variables	Before	During	After
AE	Omission errors	1.22 ± 0.83	1.67 ± 1.66	1.33 ± 1.87
	Commission errors	1.22 ± 0.67	0.11 ± 0.33	0.22 ± 0.67
	d′ (d-prime)	5.09 ± 1.01	6.63 ± 1.36	6.88 ± 1.47
	RT (ms)	401.00 ± 62.92	372.56 ± 65.28	358.22 ± 52.94
	RTV (ms)	8.68 ± 2.23	8.23 ± 2.30	8.64 ± 2.65
LE	Omission errors	4.33 ± 3.94	1.89 ± 1.69	4.11 ± 3.95
	Commission errors	1.44 ± 1.33	0.56 ± 0.88	1.00 ± 0.71
	d′ (d-prime)	4.47 ± 1.03	6.27 ± 1.13	4.79 ± 1.12
	RT (ms)	379.00 ± 53.70	379.67 ± 54.35	378.89 ± 56.37
	RTV (ms)	9.51 ± 3.22	10.67 ± 3.16	9.90 ± 3.15
SE	Omission errors	5.67 ± 5.05	4.78 ± 3.96	5.67 ± 4.36
	Commission errors	0.33 ± 0.71	0.67 ± 0.71	0.89 ± 1.17
	d′ (d-prime)	5.79 ± 1.41	5.15 ± 1.23	5.23 ± 1.27
	RT (ms)	349.22 ± 70.76	345.78 ± 44.53	353.67 ± 56.49
	RTV (ms)	8.58 ± 4.46	9.56 ± 2.94	9.97 ± 4.18

AE, alternating frequency; LE, low frequency; SE, sham electrostimulation; RT, response time; RTV, response time variability.

contrast tests comparing mean scores across time periods (i.e., before vs. after, before vs. during, after vs. during) for each of the three groups, in line with the primary goals of the study, including parameters of ERP and ICs (latencies and amplitudes) in both conditions (go and nogo cues).

Results

Behavioral Performance

Table 1 shows the means and standard deviations of the d′, commission errors, omission errors, RT, and RTV scores of the attention task for the three groups, and in Table 2 the results of ANOVA with repeated measures.

The results for d′ are shown in Figure 3 and Table 2. There were significant main effects for Group ($F[2,27] = 7.394$, $P = 0.003$) and Time ($F[2,27] = 3.487$, $P = 0.048$), and importantly there was a Group × Time interaction ($F[4,27] = 3.554$, $P = 0.013$) whereby relative to the control group stimulation in both AE and LE groups resulted in higher d′, which indicates increased perceptual sensitivity (contrast tests, $t[24] = 2.538$, $P = 0.018$ and $t[24] = 1.926$, $P = 0.066$, respectively). Furthermore with AE the increase in d′ with stimulation ($t[24] = 2.532$, $P = 0.018$; in Figure 3, t1) was sustained poststimulation ($t[24] = 2.932$, $P = 0.007$; in Figure 3, t2), whereas with LE the increase with stimulation ($t[24] = 3.494$, $P = 0.002$; in Figure 3, t3) was not sustained poststimulation ($t[24] = -2.884$, $P = 0.008$; in Figure3, t4; nonsignificant before vs. after stimulation, $t[24] = 0.611$, $P = 0.547$; in Figure 3, t5). Moreover, the consequent difference between the AE and SE groups poststimulation showed higher d′ scores following AE stimulation ($t[24] = 2.695$, $P = 0.013$, contrast test).

For omission errors there was only a Group effect ($F[2,27] = 4.347$, $P < 0.024$), without significant effects of Time ($F[2,27] = 1.727$, $P = 0.189$) or a Group × Time interaction ($F[4,27] = 1.210$, $P = 0.319$). The Group effect was attributable to the higher omission errors overall in the control group, as shown in Table 1, which were also higher at baseline ($P = 0.055$, Bonferroni). On the other hand, the commission errors, shown in Figure 4, disclosed both a tendency toward an effect of Time ($F[2,27] = 3.166$, $P = 0.051$) and importantly a significant Group × Time interaction ($F[4,27] = 2.857$, $P = 0.033$), which was due to a reduction in errors with repetition in both electroacupuncture groups. The effects of

Table 2 The effects of Group and Time (before, during, after electrostimulation) on the attention task with two-way repeated measures ANOVA

	Source	df	F	*P*
d′ (d-prime)	Group	2	7.394	0.003**
	Time	2	3.487	0.048*
	Group × Time	4	3.554	0.013*
Commission errors	Group	2	2.090	0.146
	Time	2	*3.166*	0.051
	Group × Time	4	2.857	0.033*
Omission errors	Group	2	4.347	0.024*
	Time	2	1.727	0.189
	Group × Time	4	1.210	0.319
RT (ms)	Group	2	0.809	0.457
	Time	2	2.013	0.157
	Group × Time	4	2.347	0.068
RTV (ms)	Group	2	0.605	0.554
	Time	2	1.034	0.364
	Group × Time	4	0.928	0.456

Group × Time indicates the interaction between group and time period.
*significance level: $P < 0.05$; **significance level: $P < 0.01$; according to Bonferroni correction.
AE, alternating frequency; LE, low frequency; SE, sham electrostimulation.

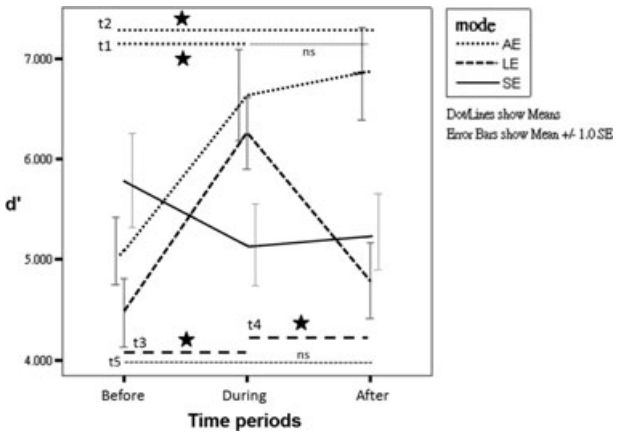

Figure 3 Electrostimulation changes on mean d′ scores (± SEM) in the attention task for both AE and LE groups relative to the SE control group (⋆ denotes $P < 0.05$; AE, alternating frequency; LE, low frequency; SE, sham electrostimulation; t1, the contrast test during vs. before stimulation in the AE group; t2, the contrast test after vs. before stimulation in the AE group; ns, not significant during vs. after stimulation in the AE group; t3, the contrast test during vs. before LE stimulation; t4, after vs. during LE stimulation; t5, before vs. after LE stimulation, ns, not significant).

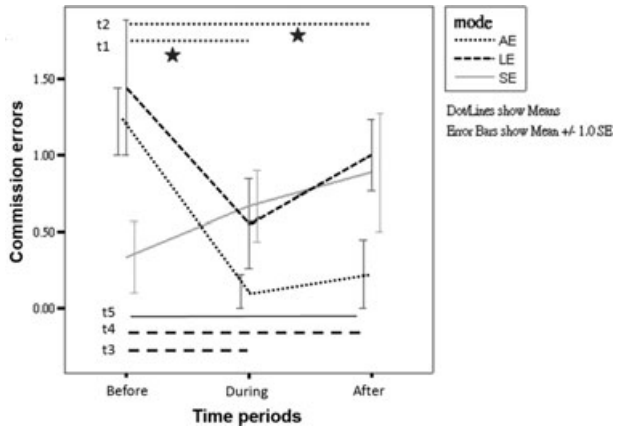

Figure 4 Electrostimulation changes on mean commission errors (± SEM) in the attention task for both AE and LE groups relative to the SE control group (⋆ denotes $P < 0.05$; t1, the contrast test during vs. before stimulation in the AE group; t2, the contrast test after vs. before stimulation in the AE group; t3, the contrast test during vs. before LE stimulation; t4, after vs. before LE stimulation; t5, after vs. before SE stimulation).

stimulation on d′ were found largely attributable to reductions in commission errors (in Figure 4 and Table 1). Then underscoring the pattern of results with d′, whereas with AE stimulation there was a decrease in commission errors (contrast test, t[24] = –4.082, $P = 0.0004$, in Figure 4, t1) which was sustained poststimulation (contrast test, t[24] = -3.674, $P = 0.001$, in Figure 4, t2), with LE there was a tendency toward a decrease in errors with stimulation (contrast test, t[24] = –1.868, $P = 0.074$, in Figure 4, t3) which was not sustained poststimulation (contrast test, t[24] = –0.934, $P = 0.360$, in Figure 4, t4).

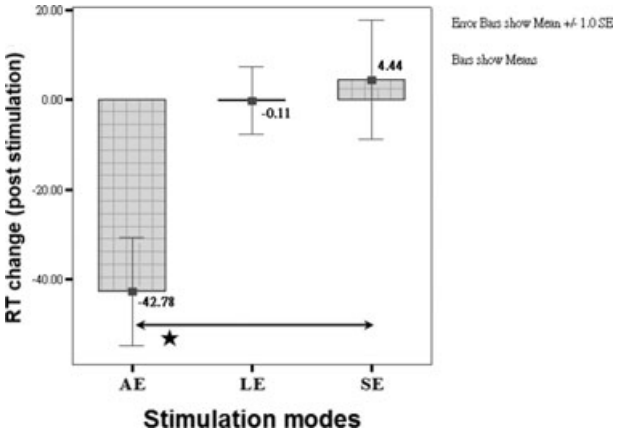

Figure 5 Postelectrostimulation changes on mean response times (± SEM) in the attention task for the AE, LE, and SE control groups (⋆ denotes $P < 0.05$; RT, response time).

Turning to the RT measures there were no significant effects of Group (Table 2, F[2,27] = 0.809, $P = 0.457$), Time (F[2,27] = 2.013, $P = 0.157$) nor was there a Group × Time interaction (F[4,27] = 2.347, $P = 0.068$). However, as can be seen in Table 1 and Figure 5, there was a mean reduction in RTs poststimulation in the AE group compared with the SE group. Exploratory *post hoc* analyses with the Bonferroni correction indicated that the reduction in RT differed significantly between the SE and AE groups poststimulation ($P = 0.023$). Regarding response time variability (RTV), there were no significant effects of Group (F[2,27] = 0.605, $P = 0.554$), Time (F[2,27] = 1.034, $P = 0.364$) nor was there a Group × Time interaction (F[4,27] = 0.928, $P = 0.456$).

ERP Data

The group grand averages of the two conditions (go and nogo) in the attention task for the midline electrodes for each time period (before, during, and after stimulation) are illustrated in Figure 6. All three groups showed no statistically reliable changes in the early ERP components (with latencies of 80–180 ms), or in the late positive components (180–420 ms), and all groups displayed a trend of decreasing amplitude, but with no statistically significant findings (see also Table 3).

Extracting Late ERP Components by Means of the ICA Method and Spatial Filters

Motor Inhibition Component

Analysis of the grand mean ERPs in response to the difference between go and nogo cues revealed a relatively large frontocentral positive deflection in all groups, especially in the AE group (left columns of Figures 7A and 8A). Interestingly, for the AE group at Fz, Cz, and Pz, the motor inhibition component extracted by the ICA method and spatial filters had a significantly decreased peak

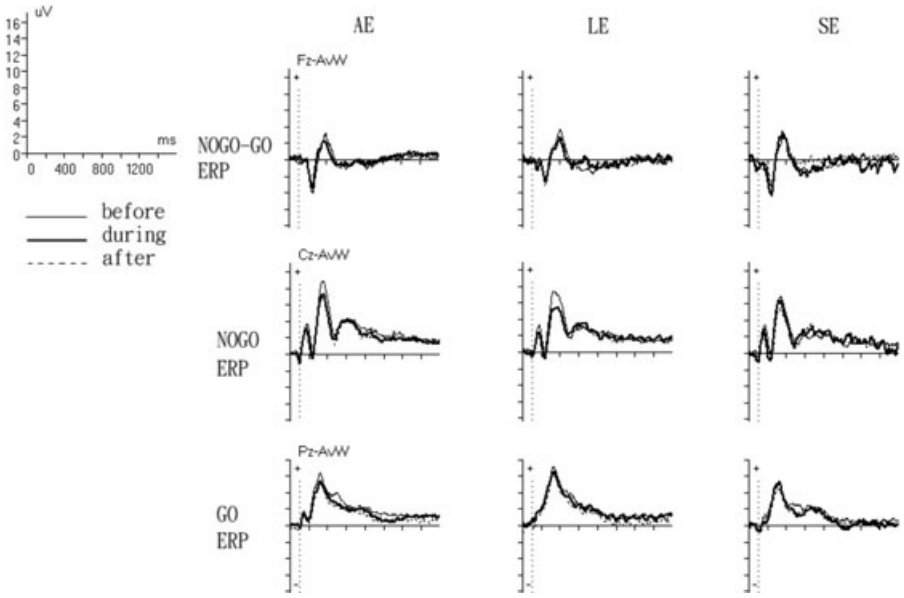

Figure 6 Grand average ERPs for each group and time block for the midline electrodes in the attention paradigm. A frontally distributed negative ERP component had greater amplitude for nogo in comparison to go stimuli and was associated with response inhibition in go-nogo paradigms (upper panel). No significant changes in amplitudes and latencies among three groups and three time periods (before, during, and after stimulation) were found. (See also Table 3.)

Table 3 Means and standard deviations for the visual attention ERP measures in each group before, during, and after electrostimulation

Group	go/nogo	Before variables	During	After
AE	Pz go amplitude	6.07 ± 2.20	4.96 ± 2.28	4.77 ± 2.12
	Pz go latency	323.78 ± 10.60	321.56 ± 13.33	322.44 ± 8.82
	Cz nogo amplitude	9.22 ± 3.59	7.23 ± 2.49	7.21 ± 2.19
	Cz nogo latency	348.67 ± 17.89	348.22 ± 16.38	344.67 ± 24.49
LE	Pz go amplitude	7.10 ± 3.23	6.39 ± 2.78	6.24 ± 2.95
	Pz go latency	321.56 ± 21.49	320.22 ± 24.13	317.56 ± 24.29
	Cz nogo amplitude	8.39 ± 5.35	6.37 ± 4.33	6.76 ± 3.81
	Cz nogo latency	362.44 ± 31.52	363.78 ± 31.31	355.33 ± 33.97
SE	Pz go amplitude	5.20 ± 2.95	5.40 ± 2.28	4.36 ± 1.80
	Pz go latency	324.44 ± 16.49	328.67 ± 19.34	326.22 ± 24.05
	Cz nogo amplitude	7.01 ± 4.52	6.71 ± 3.88	5.37 ± 4.27
	Cz nogo latency	354.00 ± 15.17	351.33 ± 22.05	342.44 ± 15.61

AE, alternating frequency; LE, low frequency; SE, sham electrostimulation.

from 372 ms to 396 ms, compared with the prestimulation stage (during vs. before stimulation, $P = 0.0156$ in Figure 7; after vs. before stimulation, $P = 0.0143$ in Figure 8) [73–75].

Analysis of ICs Related to Habituation/Inattention

To evaluate if a putative habituation effect in controls would be inhibited by the stimulation with task repetition, we used the ICA method to reveal the fundamental components in the ERPs. The related ICs of ERPs were compared for the first and last task in each group. Of 11 components that were identified by the spatial filters based on the ICA from the Human Brain Indices (HBI) reference database. (http://www.mitsar-medical.com) [65], seven components responding to the "go and nogo" cues were meaningfully related to the visual attention task as follows: visual comparison component at the left temporal area, visual comparison component at right temporal area, P400 working memory component at the frontal area, P300b component at the parietal area, slow wave component at the hippocampus, P300 suppression component at the frontal area, and P400 action monitoring component at the anterior cingulate cortex (ACC) [65]. However, only

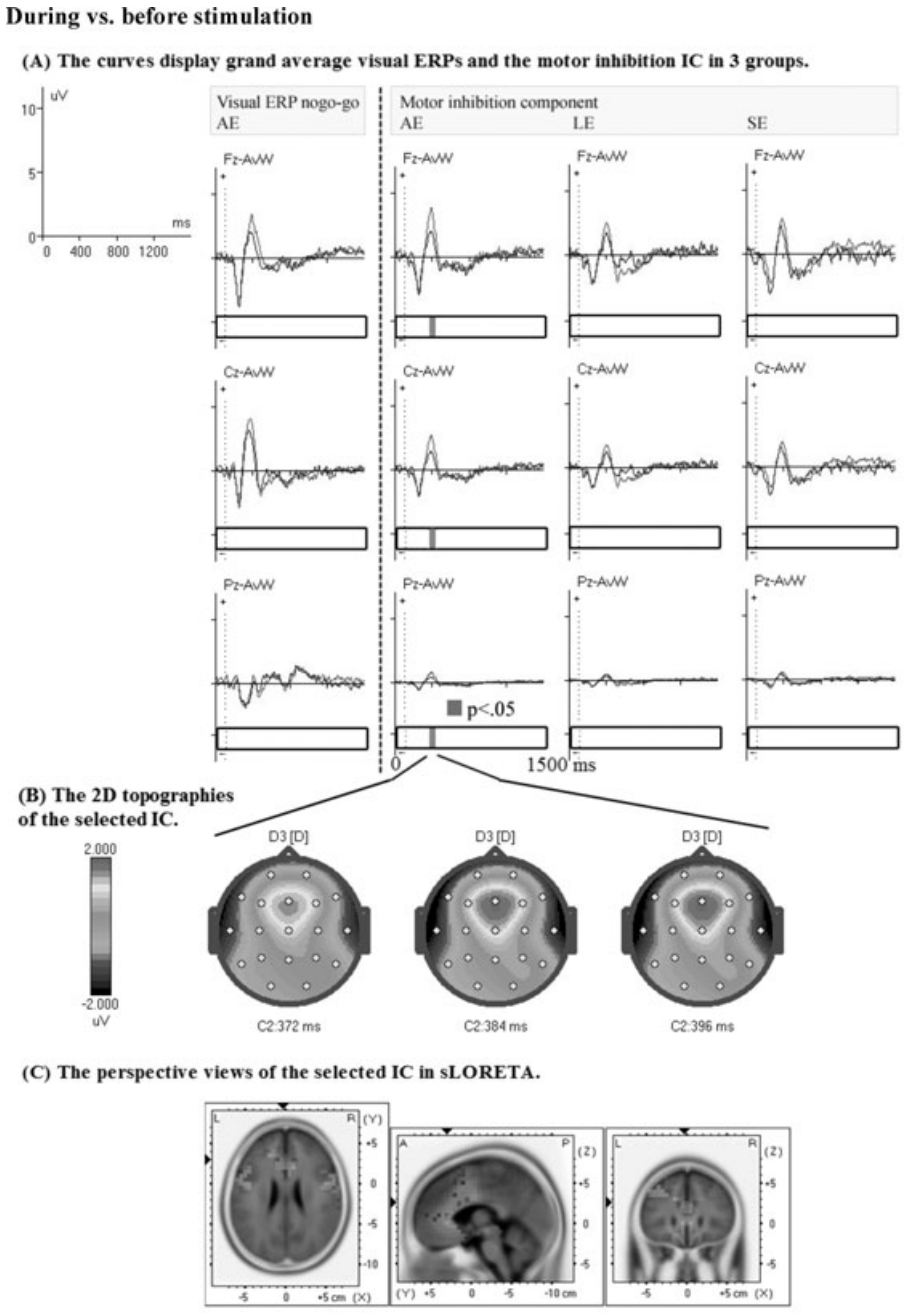

Figure 7 (**A**) Grand mean extracted motor inhibition ICs at midline scalp sites and correlated ERP of nogo-go cues, during stimulation (blue lines) compared with prestimulation (red lines) in the three groups. Red lines showed the prestimulation baseline of grand mean ERPs and grand mean motor inhibition components in the three groups. The animal pairs were the targets of the manual responses (GO cues), and nogo-go means the component difference between go and nogo cues. Superimposed blue lines gave the grand mean ERPs and grand mean motor inhibition components during electrostimulation in the three groups. (**B**) Horizontal bars below each trace represent *t*-test results from 0–1500 ms after the second stimulus onset, with values $P < 0.05$ represented in gray between 372 and 396 ms, to illustrate the time course of significant differences from the baseline in the 2D scalp maps. (**C**) The perspective views (top, sagittal, and coronal views) showed the highest density of the motor inhibition component, according to sLORETA images for cortical generators.

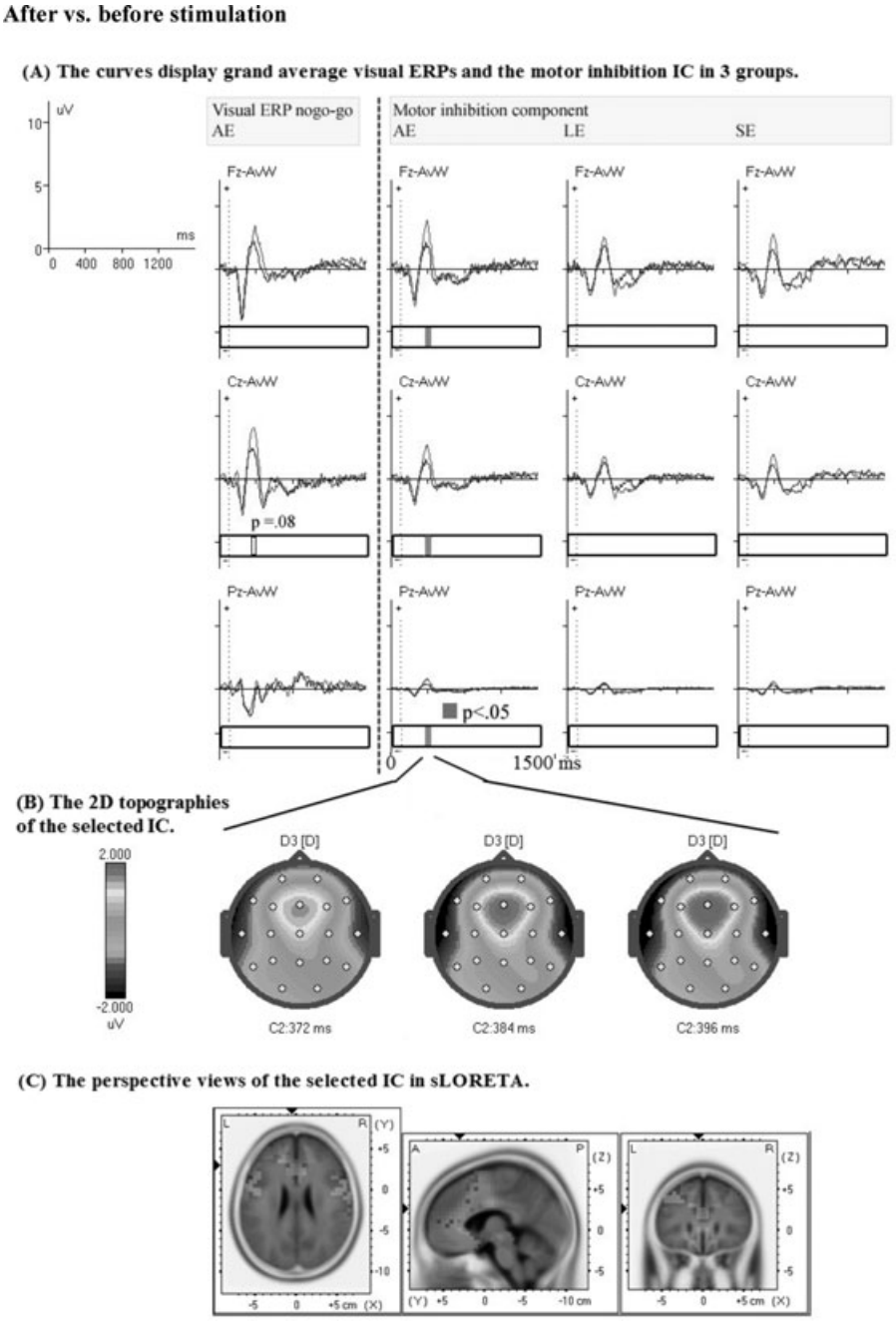

Figure 8 (**A**) Grand mean extracted motor inhibition ICs at midline scalp sites and correlated ERP of nogo-go cues, after stimulation (blue lines) compared with prestimulation (red lines) in the three groups. Layout as for Figure 7(A)–(C).

significantly changed ICs were considered further, as the goal of this report was to describe and investigate the ICA features that significantly changed by applying electroacupuncture and/or attention task repetition (details in the next paragraphs).

The ICA decomposition of the attention task revealed similar components in the three conditions. Between-group differences in mean IC topographies in the prestimulation stage were barely visible, suggesting a good reproducibility of the component characteristics [76]. However, only with the control group did the differences between the first and the third repetition in mean IC topographies show fatigue according to time-on-task effects showing significantly decreased amplitudes of the components [77–79,80]. Four components showed obvious differences, including the left visual comparison component, the P400 action-monitoring

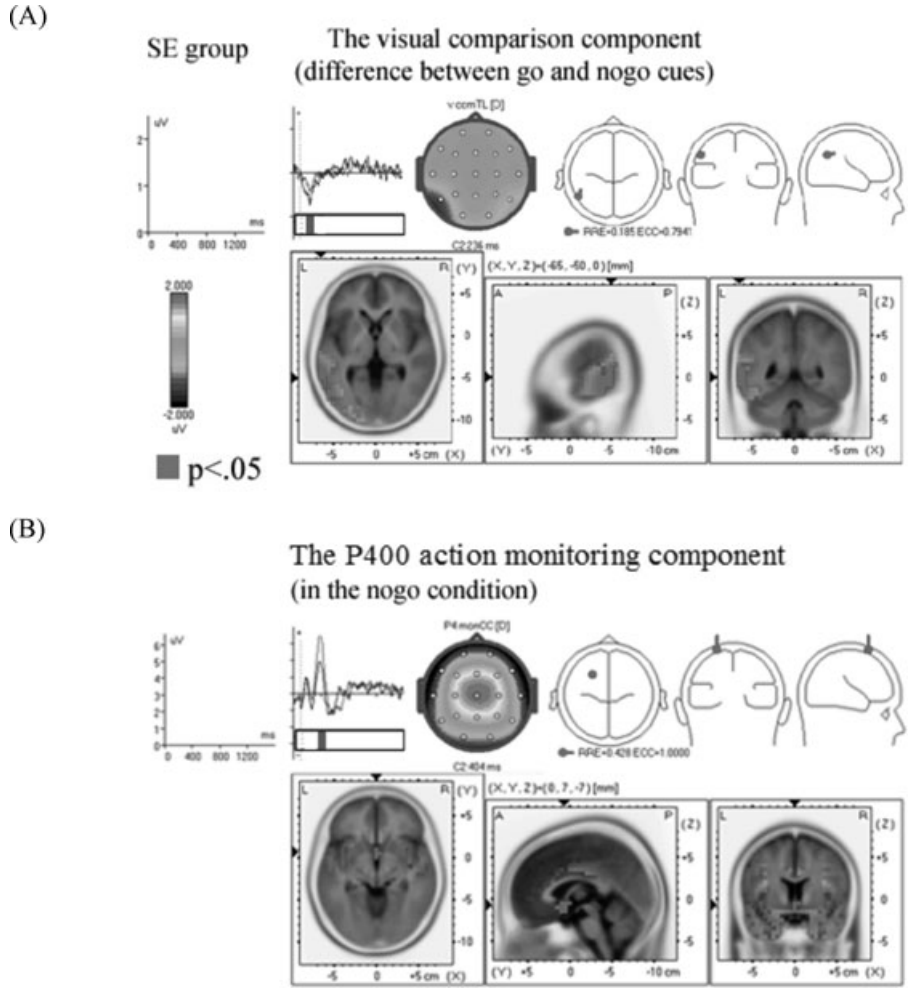

Figure 9 The independent components difference between the first and third task repetition in the sham stimulation group. (**A**) The visual comparison component difference between go and nogo cues. (**B**) The P400 action monitoring component in the nogo condition. The upper row of the panel for each component shows the grand mean component in amplitude-time plot at Cz (upper left), the scalp topographic map (upper middle), and the single equivalent current dipole locations for each component (upper right). The lower row shows the highest density of each component, according to sLORETA images, from three different perspectives (top, sagittal and coronal views). Each red line shows the grand mean component of the first attention task. Each superimposed blue line gives the grand mean component of the repeated third task. Horizontal bars below each trace represent *t*-test results from 0–1500 ms post second stimulus onset, with values $P < 0.05$ represented in gray, to illustrate the time course of significant differences between the first and the third repeated tasks.

component, the P400 working memory component, and the passive auditory P300 component. The average characteristics of the components as identified in the control group from the beginning to the end of the three tasks are shown in Figures 9 and 10, with details in the next paragraphs.

Visual Comparison Component, Left: The normalized grand-mean component in Figure 9, (Figure 9A, upper row), revealed a large negative deflection between 100 and 400 ms post second stimulus onset, peaking around 236 ms ($P < 0.05$), with a left temporal topography. The significant change of this component in left temporal topography was also projected on to a mean- magnetic resonance imaging (MRI) brain image (Montreal Neurological Institute, Canada), according to the sLORETA images of the components (Figure 9A, bottom row) [65,81].

P400 Action Monitoring Component: As illustrated in Figure 9(B), the second component of interest was labeled the P400 action monitoring component in the ACC area due to its time course and topography, which was characterized by a later and slower ERP positivity from 260 to 520 ms with a peak latency around 400 ms (Figure 9B, upper row). The P400 action monitoring component location was in deep brain frontocentral regions through the ACC area (Figure 9B, bottom row) [65,82]. The characteristics of the significantly decreased amplitude of the P400 action monitoring component ($P < 0.05$, around the peak) outlined in Figure 9(B)

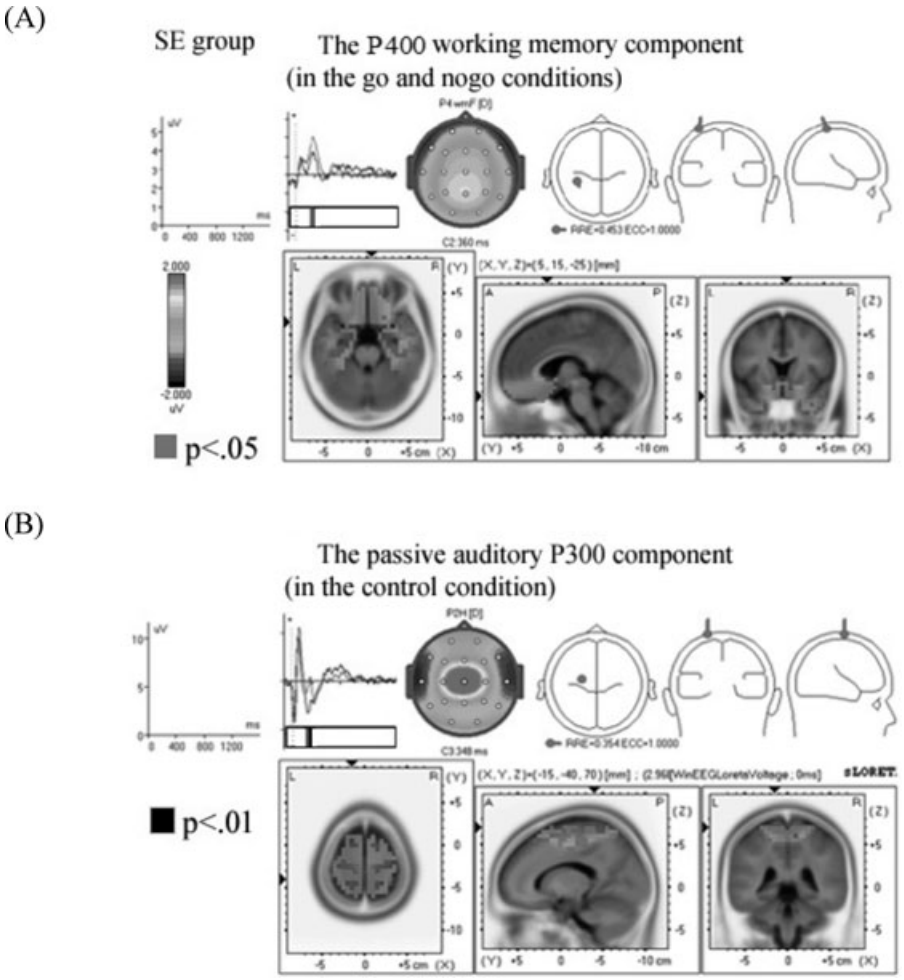

Figure 10 The independent components difference between the first and third task repetition in the sham stimulation group. (**A**) The P400 working memory component in both the go and nogo conditions. (**B**) The passive auditory P300 component in the control condition. Same layout as for the panels in Figure 9(A) and (B) with values $P < 0.05$ and $P < 0.01$ represented in gray and black, to illustrate the time course of significant differences between the first and the third repeated tasks.

strongly suggested a relation between fatigue with task repetition, a time-on-task effect [76,80].

P400 Working Memory Component: The P400 working memory component presented with a positive double-peak morphology between 148 and 540 ms post second stimulus onset (peak latency around 360 ms; Figure 10A, upper row). This projected component on sLORETA images appeared to be more accurate than the 2D scalp map for assessing the spatial distributions of current density in deep sources. The P400 working memory component location was in the deep inferior prefrontal region, around the hippocampal area (Figure 10A, bottom row) [65,83]. The characteristics of the P400 working memory component mostly demonstrated a relation between fatigue with task repetition with a decline in amplitude ($P < 0.05$, around the peak).

Passive Auditory P300 Component: As illustrated in Figure 10(B), the passive auditory P300 component includes auditory N1/P2 peaks [84], thus serving as a good indicator of the functioning of the auditory system in the visual attention task [85]. The peak of the passive auditory P300 component is around 348 ms and lasting roughly 900 ms. The passive auditory P300 responding to deviant auditory stimuli can be elicited without active attention. The 2D topography and the sLORETA images showed the highest density over the central scalp electrodes (Figure 10B, bottom row) [65,84,85]. The characteristics of the passive auditory P300 component possibly showed a significant relation between fatigue with task repetition with a declined amplitude of the passive auditory P300 component ($P < 0.01$, around the peak) in the present study, also as a function of time-on-task [76,80].

Discussion

The primary purpose was to explore the effects of electroacupuncture stimulation on a repetitive visual continuous performance

attention test and accompanying attention-related ERPs using behavioral performance indexes and ERP components extracted by the ICA method. Whereas a number of EEG studies have explored acupuncture effects without the popular ERP methodology [12,86–89], our current investigation was designed to complement these through the neglected field of topographical EEG, and also to learn more about the recent development of electrical stimulation. It was of particular interest to determine whether putative benefits would outlast stimulation, and whether stimulation with alternating high and low frequencies would be superior to low-frequency stimulation. It was hypothesized that stimulation would result in a significant behavioral change with increased sensory sensitivity (d′), largely due to a decrease in errors of commission, as found previously with university students performing the visual continuous performance task [71,90]. Students tend to be highly motivated to attend, producing few errors of omission, whereas the motivation to achieve may lead to over eagerness, resulting in impulsive errors of commission. It was further hypothesized that their performance would be reflected in ERP components with different types of ERPs generated on 'go' versus 'nogo' trials. Another purpose of this study was to examine if a putative habituation effect in controls would be inhibited by stimulation with task repetition. For this purpose response synchronized ICs of ERPs were compared for the first and last task in each group.

Behavioral Results

There was some suggestion of differences in commission errors, but given that the *P*-value was not significant with the conservative Bonferroni adjustment, caution must be applied and further research is warranted. However, $\underline{d}'$ was significantly changed differentially by parameters of stimulation (Table 2), particularly in relation to attention during and after stimulation with alternating frequencies (Figure 3).

The findings overall indicated that stimulation with alternating frequencies was superior to low-frequency stimulation in having sustained effects during the task, benefits which continued poststimulation. In contrast, low-frequency stimulation while effective during stimulation did not produce sustained benefits. These effects on the visual sustained attention task were disclosed through higher $\underline{d}'$ scores [53,91]. As anticipated, the improved $\underline{d}'$ score was largely due to a reduction in commission errors. RT was less definitively influenced, though exploratory *post hoc* tests confirmed shorter RTs following alternating frequency stimulation in the poststimulation condition when compared with sham stimulation.

ERPs to the Go and Nogo Stimuli

Compared to the prestimulation stage, the grand average ERPs showed a trend of decreasing peak amplitudes of the late components because of task repetition, but no changes in those early components having latencies between 80 to 180 ms. Previous studies using nonaffective targets have reported decreased P300 amplitudes at fronto-central sites both as a function of time-on-task and with sequence repetition, [77–79,80]. Another study employing unpleasant, neutral, and pleasant stimuli has reported that P300 amplitude decreased with repetitive picture processing [92]. In the current study the stimuli were mainly nonemotional and hence the results were in line with previous studies, notwithstanding the novel introduction of acustimulation

Application of ICA, Spatial Filter, and sLORETA

Applying ICA with spatial filtration disclosed a variety of interesting results, which confirm and extend efforts to decompose ERP components recorded during the visual attention task [93]. Mathematically, ICs are often characterized by scalp maps fitting the projection of a single equivalent current dipole, which is compatible with each presumed component reflecting synchronous cortical local field activity of a connected network. However, only a few components can be approximately calculated by a single dipole because some components are most likely to be generated by distributed neuronal circuits. Therefore standardized sLORETA images were used instead of dipole approximations. Overall the present findings strongly suggest that the main features of averaged ERP components can be successfully decomposed from ERP data via ICA decomposition combined with spatial filters (from HBI database) for each group and each time period, especially for the pre- versus poststimulation comparison. The components reflected motor inhibition, visual comparison, P400 action monitoring, working memory, and passive auditory P300 components.

Acupuncture Effect Induced by Stimulation in the Real versus the Sham Group

The typical HeGu and NeiGuan (LI-4 and P-6) acupoints are among the traditional points used in modulating cortical plasticity, relieving pain, and treating nausea and vomiting [12,57,94]. The HeGu acupoint lies at the midpoint between the first and second carpal bones of the first web space on the dorsal side, and the NeiGuan acupoint is located on the anterior surface of the wrist, approximately 3 cm proximal to the wrist between the tendons of the flexor carpi radialis and the palmaris longus, next to the median nerve. These junctures are full of peripheral nerve extensions from the sensory nerve and muscle tendons [95], and with lower focal transcutaneous resistance they can provide effective electrical stimulation without much current. In contrast, the sham (fake) electroacupuncture at the same acupoints (placebo electrostimulation), generates insufficient sensory input to cortex. Thus the observed changes of behavior and the motor inhibition component in the ERP could be due to the differences in the nerve conduction and excitability of stimulated acupoints of the two real electroacupuncture groups and the selected minimal stimulation in the sham group [57]. Certainly the differential stimulation effects between real versus sham stimulation on the same sites in behavioral performance and changes in ICs encourage the use of sham stimulation as a control for the study of brain function and associated acupuncture effects.

Acupuncture Effect Induced by Stimulation in Alternating Frequency Mode versus Low-Frequency Mode

Our study confirmed that only stimulation with alternating frequencies (5/100 Hz), but not with a low frequency delivered at 5 Hz, had the sustained poststimulation effect in improving d′ scores and decreasing mean commission errors. Low stimulation at 5 Hz had only short-lived benefits. In addition, compared to the baseline without stimulation, alternating stimulation induced a significantly decreased motor inhibition component during stimulation and poststimulation, which theoretically was compatible with improvements in commission errors, which reflect motor impulsivity.

For clinical practice, the result of a prolonged effect due to alternating high and low frequencies has become an important issue for treatment [56]. A recent study with resting functional magnetic resonance imaging (fMRI) data using a probabilistic ICA method demonstrated for the first time that the poststimulation effects of acupuncture can enhance the spatial extent of resting brain networks [11]. Interestingly, such sustained poststimulation effects have been hypothesized to alleviate pain by altering neurotranmission in the CNS in both animals and man [1,96]. Differential release of opioid peptides in the CNS by electroacupuncture stimulation has been noted, with a low frequency of 2–15 Hz triggering the release of enkephalins and Beta endorphins, and a high frequency of 100 Hz stimulation increasing the release of dynorphin at the spinal cord level [1]. A combination of both frequencies with an alternating current of 2 and 100 Hz may allow synergistic interaction among the neurotransmitters and so provide a more powerful effect than sham stimulation [57,94]. Napadow et al. with fMRI have claimed that the limbic system is central to acupuncture effects regardless of the specific acupuncture modality, although some differences do exist in the underlying neurobiologic mechanisms for different modalities. The findings may also provide hints for optimizing acupuncture in clinical applications [97].

Further Potential Clinical Applications

Although most of the studies of electroacupuncture stimulation have explored the role of acupuncture in analgesia, neuroimaging research has also revealed possible brain networks and regions for potential influence on attention and memory [11,12,63,64,97]. Manual stimulation showed increased regional cerebral blood flow (rCBF) mainly in the parahippocampal gyrus, premotor area, frontal and temporal areas bilaterally, and the ipsilateral globus pallidus [98]. In a recent report of electroacupuncture-induced analgesia examined by fMRI, several areas with positive correlation of analgesic effects for low-frequency stimulation included the contralateral motor area, the supplementary motor area, and the ipsilateral superior temporal gyrus. In contrast with high-frequency stimulation the response occurred in the contralateral inferior parietal lobule, ipsilateral ACC, nucleus accumbens, and pons [64,99]. Functional MRI has demonstrated the CNS pathways involved in acupuncture stimulation. Even the subcortical gray structures, hypothalamus-limbic system, and hypothalamus-pituitary-adrenal (HPA) axis have been related to electroacupuncture stimulation [63,100,101]. In the case of low-frequency stimulation, high activation has been elicited over the hypothalamus and primary somatosensory-motor cortex, with deactivation over the rostral segment of ACC [63].

The findings of our study also support the assumption that electroacupuncture stimulation has an effect on specific brain areas, and the improved performance in cognition is possibly related to enhanced cortical activity. While previous studies have demonstrated a sustained poststimulation effect for pain relief, gastric mobility, and heart rate variability (HRV) [102–104], to our knowledge no prior published research has examined sustained attention during stimulation and poststimulation periods in healthy young adults. This conclusion followed a search of nine bibliographic databases for the effects of TENS on nonpain related cognitive and behavior which found only reports on patients [105].

The Guidelines for Electroacupuncture Safe Practice in Dual-Site Electroacupuncture Stimulation of the Experimental Design

In clinical practice, the more distal acupoint location of the electrodes on hands and wrists seems much more practical than the proximal location of the limbs, paraspinal muscles, and neck or head regions. Our design with a pair of acupoints on each hand followed the guidelines for safe practice recommended by the British Medical Acupuncture Society (BMAS) to avoid adverse events. Especially, electroacupuncture should not be applied such that the current is likely to traverse the heart. If the application of electrostimulation is likely to cross the heart (e.g., from one shoulder to the other shoulder [106]), this placement is prohibited. A study has also reported that electrical fields generated by pairs of needles below the knee or elbow do not create a detectable spread of the currents along the limb or into the chest [106]. The safety guidelines are rarely mentioned in scientific reports.

Limitations and Recommendations for Future Research

Notwithstanding the beneficial outcome on sustained attention that we have demonstrated, our study has potential limitations or at least issues warranting further examination. First, an optimal washout period of the neurobiological effects generated by stimulation remains unknown. The effective poststimulation period was for a minimum of 30 min in our study, similar to the report of Claydon et al. using pressure pain threshold [102]. Second, the optimal sites for influencing cognition have not been systematically examined. HeGu (Li4) and NeiGuan (P6) are the well-studied acupoints, but other acupoints such as Zusanli (St36) and Taichong (Liv3) might be helpful adjuncts for improving cognitive function. Third, the relative contribution of the mechanism for the synergistic action produced by different combinations of neuropeptides is still not well understood, and therefore, the effectiveness of alternating frequency stimulation must be verified with neuroimaging. Meanwhile, various stimulation frequencies may involve different mechanisms. Several neurotransmitters such as serotonin and

dopamine are also believed to contribute to attention and memory systems [107–109]. It is not clear, however, to what extent these neurotransmitters are involved and how they are affected during and after electrical stimulation. Further research should be conducted to combine the behavioral, electrophysiological, and neurochemical modulation data.

Regarding the blinding of participants, first, we asked them to perform and focus on the repetitive visual attention task, and not pay attention to the sensation induced at the stimulated site. Second, the requirement of recruiting subjects was that all subjects had no experience about electroacupuncture prior to our testing. Complying with ethical considerations, although all subjects were blind to the stimulation mode and effect, they were told that the machine could generate transcutaneous stimulation on the acupoints of the hands with various frequencies, which may or may not give a sensation. However, because subjects had no experience of electrostimulation, they were blinded to the relationship of stimulation modes and effects. Importantly, only the intensity parameter of stimulation in the sham group was different from the real electroacupuncture groups, and possibly any emotional reaction to the thought of minimal tactile sensation was unlikely to influence responding; as mentioned earlier the sham stimulation itself has been shown not to affect sensory cortex [57,63].

Finally, electroacupuncture stimulation presented in this study is one method for modulating neuronal processing in order to improve cognitive performance. This may be useful in the range of neurological and psychopathological conditions mentioned above where the continuous performance paradigm has disclosed deficits [37,39,105]. Two studies related to the effects of TENS on cognition and behavior showed a moderate beneficial influence on cognitive functions in children with ADHD [110] and in aging [111].

EEG-neurofeedback is another approach [37,90,112]. In addition, recent emerging approaches combine feedback techniques and stimulation strategies for exploring more effective training protocols than either alone [113,114]. A just completed unpublished study has disclosed evidence for electroacupuncture stimulation assisting EEG-biofeedback training in the improvement of attention and memory performance and fundamental cortical electrophysiological activities as shown previously [71,72,115].

Conclusions

This single-blind randomized placebo-controlled study showed that electroacupuncture stimulation with alternating frequencies on pairs of acupoints of both hands resulted in significantly better sustained behavioral performance and sustained cortical activation in a repeated visual continuous attentional performance task than low-frequency stimulation, which in turn was superior to placebo. No obvious adverse effect in healthy subjects was noted. Evidence was provided that ICA with spatial filtration, applied to ERP data, successfully decomposed the spatiotemporally overlapping ERPs into a range of underlying EEG processes whose localization was congruent with a range of behavioral functions: visual comparison, P400 action monitoring, working memory, and passive auditory P300. The alternating frequency stimulation could be an adjunct for helping adults successfully enhance their sustained attention and inhibit competing motor responses both during and poststimulation, indicating its potential therapeutic benefit for psychiatric disorders with compromised attention and cognition. When the baseline was compared with the prestimulation and poststimulation period in the control group with the placebo stimulation, the IC-derived ICs disclosed evidence of habituation. The absence of habituation in the experimental groups suggests a potentially successful activation for preventing fatigue. Further randomized trials with a larger sample size will be conducted to compare and combine electroacupuncture stimulation with a more established modality, such as EEG-biofeedback. Interestingly, these further trials will clarify the role of applied acustimulation on self-regulation, cognitive function, and cortical activation.

Acknowledgments

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Conflict of Interest

The authors have no conflict of interest.

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