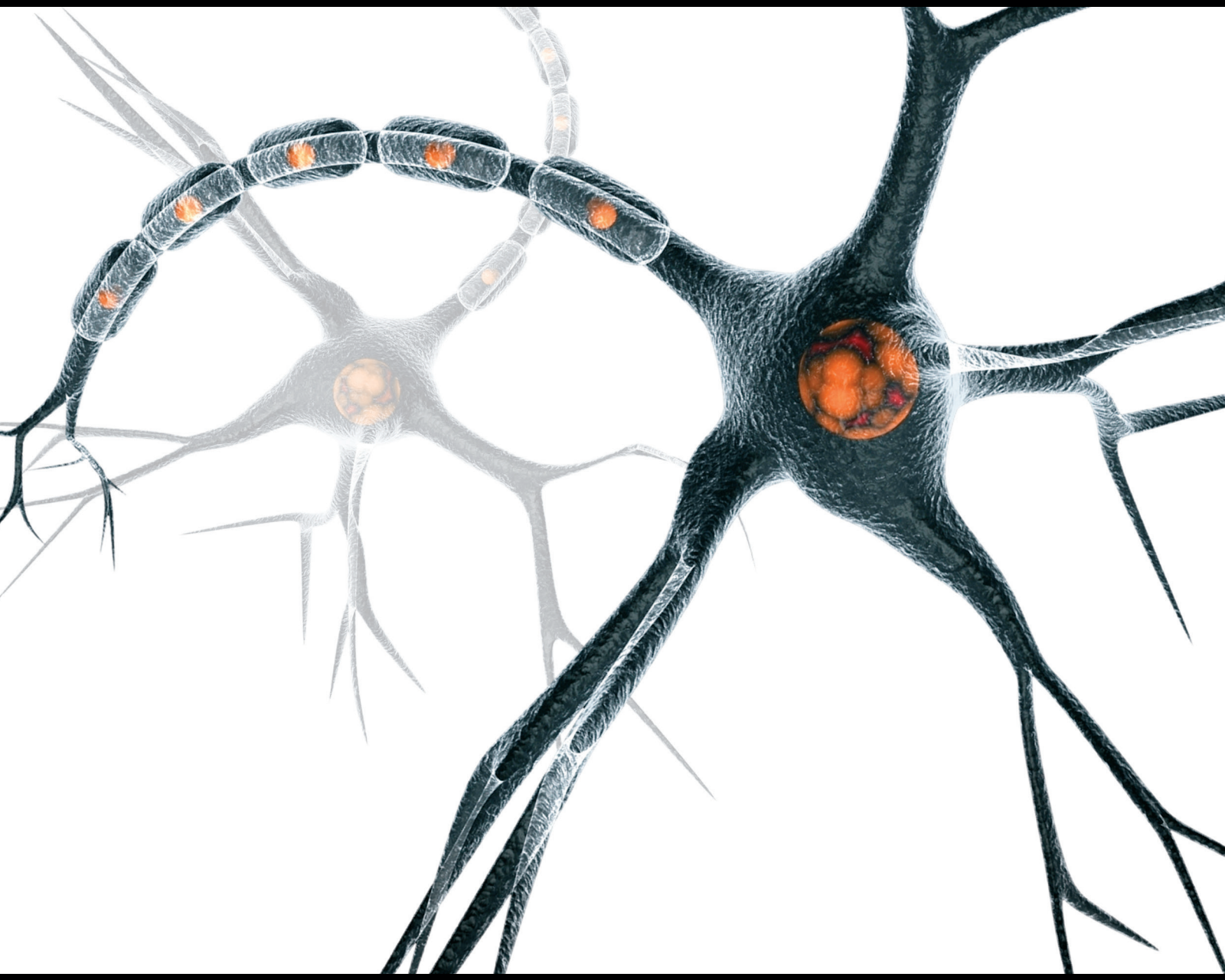
Neural Plasticity

# Brain and Behavior Plasticity: From Fundamental Science to Health Outcomes

Guest Editors: Keh-chung Lin, Steven L. Wolf, Chetwyn Chan, Ching-yi Wu, and Ching-po Lin



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# Editorial Board

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*Editorial*

# Brain and Behavior Plasticity: From Fundamental Science to Health Outcomes

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Human brains are highly plastic throughout the lifespan, even after brain injuries. The possible modulation of functions due to neural plasticity in various brain regions contributes to the learning and adaptation of unlearnt as well as new behaviors. Over the past decade, research on brain-behavior relationships has grown exponentially. In addition to behavioral assessments, electrophysiology and neuroimaging methods have been widely used to examine the neural networks, structural and functional abnormalities, and the effects of the therapeutic training in aged adults or individuals with neurological disorders. The five contributions to this special issue address the relationships between brain and behavior and have implications for present and future research and practice in neurorehabilitation.

Data presented in the article titled "An Influence of Birth Weight, Gestational Age, and Apgar Score on Pattern Visual Evoked Potentials in Children with History of Prematurity" by M. Michalczuk et al. suggests that low birth weight, early gestational age, and poor baseline output are possible predictors for the development rate of brain function. The article titled "Age-Related Reduced Somatosensory Gating is Associated with Altered Alpha Frequency Desynchronization" by C.-H. Cheng et al. attempts to elucidate the neural mechanisms of age-related sensory gating decline in the somatosensory system. By using a paired-pulse protocol and time frequency analysis, the authors found that insufficient stimulus 1 induced alpha oscillations lead to a less-suppressed stimulus 2 evoked response.

The article titled "Coincidence Anticipation Timing Performance during an Acute Bout of Brisk Walking in Older Adults: Effects of Stimulus Speed" by M. J. Duncan et al. reported an age-related decline in anticipation timing performance when performing dual tasks. They have also reported that the stimulus speed of the secondary task plays an important role in the performance of older adults. Data from the article titled "Neural Plastic Effects on Cognitive Training on Aging Brain" by N. T. Y. Leung et al. suggested the presence of an experience-dependent neural plasticity following a thirteen-week training program of attention and working memory in older adults. This work also indicates that initial cognitive status may not limit the potential of neural plasticity at an older age. The article titled "Restoration of Central Programmed Movement Pattern by Temporal Electrical Stimulation-Assisted Training in Patients with Spinal Cerebellar Atrophy" by Y. Z. Huang et al. reported a novel 4-week training program developed to correct the aberrant triphasic EMG patterns in these patients resulting in restoration of facilitation of antagonist muscle activity.

The articles published in this special issue provide new insights into the neural plasticity in terms of the brain-and-behavior relations and contribute to extension of research on neurobehavioral rehabilitation. Further research is needed to

verify the value of the knowledge derived from this collection of scientific endeavors.

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*Research Article*

# Neural Plastic Effects of Cognitive Training on Aging Brain

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Increasing research has evidenced that our brain retains a capacity to change in response to experience until late adulthood. This implies that cognitive training can possibly ameliorate age-associated cognitive decline by inducing training-specific neural plastic changes at both neural and behavioral levels. This longitudinal study examined the behavioral effects of a systematic thirteen-week cognitive training program on attention and working memory of older adults who were at risk of cognitive decline. These older adults were randomly assigned to the Cognitive Training Group ($n = 109$) and the Active Control Group ($n = 100$). Findings clearly indicated that training induced improvement in auditory and visual-spatial attention and working memory. The training effect was specific to the experience provided because no significant difference in verbal and visual-spatial memory between the two groups was observed. This pattern of findings is consistent with the prediction and the principle of experience-dependent neuroplasticity. Findings of our study provided further support to the notion that the neural plastic potential continues until older age. The baseline cognitive status did not correlate with pre- versus posttraining changes to any cognitive variables studied, suggesting that the initial cognitive status may not limit the neuroplastic potential of the brain at an old age.

## 1. Introduction

Neural plasticity refers to the capacity of our brain to change in response to internal demand and/or external experience [1]. Burgeoning research has corroborated that the neural plastic changes induced in our brains and behaviors are specific to the experiences (e.g., [2–7]). For instance, the London taxi drivers who have protracted experience in driving around the city with complex road infrastructure demonstrated significant increases in brain structural volume in the posterior hippocampus, which is implicated in storing spatial representation of the environment, suggesting that intensive experiences with spatial navigation can induce specific neural plastic changes in the corresponding brain region [3]. Similarly, Lee et al. [6] have identified distinct patterns of neural activation associated with different forms of meditation practice, namely, focused-attention meditation (FAM) and loving-kindness meditation (LKM), during the performance of the sustained attention task. While FAM is a form of meditation practice with a heavy emphasis on focusing attention on a particular object [8], LKM stresses on the cultivation of a state of universal love and compassion as to relieve pain and

suffering for the self and others [9]. Their findings revealed that FAM practitioners (both experts and novices) showed significantly greater neural activation in the attention-related network when engaging in the sustained attention task, whereas similar neural activation was not observed in the LKM practitioners. The dissociable neural pattern associated with FAM and LKM indicated that meditation, as a form of mental exercise, could induce domain-specific neural plastic changes that accord with the form of meditation practice [6]. These findings offer an insight that perhaps a cognitive experience can be designed to specifically target triggering experience-dependent neural plastic changes in the cognitive domain of interest.

Yet, our brain, albeit malleable, inevitably undergoes certain degrees of age-associated cortical degeneration at the molecular level as age advances. For instance, significant reduction in global and regional gray matter volume, particularly in the prefrontal and medial temporal regions (e.g., [10–13]), as well as age-related alterations in the functional connectivity of the default mode network (e.g., [14, 15]) have been consistently reported in older adults. These age-related neural changes may cause cognitive deterioration in the aging brain.

Substantial research has yielded evidence of age-related decrements in attention and working memory performance (e.g., [16–20]). Mani et al. [21] observed that older adults committed significantly more errors than younger adults when performing a task on sustained attention, suggesting that the ability to sustain attention (in terms of response accuracy) was compromised during the natural aging process. It has been speculated that older adults, in order to compensate for their deficits in attentional performance, are required to recruit additional cognitive resources [20, 22]. Working memory also declines with aging. Mattay et al. [23] observed that the performance of older relative to younger adults declined with increased working memory load. In terms of long-term memory, profound changes in episodic memory have also been evidenced [24, 25], which can be attributed to the age-associated degeneration in the medial temporal regions, especially the hippocampus. Findings from a six-year longitudinal study revealed that hippocampal atrophy and a reduction of neural activation in the hippocampus were only identified in older adults demonstrating declines in memory performance but not in those with intact memory function [26]. Findings of all these studies highlight the natural course of cognitive degeneration with aging. Research on neuroplasticity-based intervention for age-associated cognitive changes is timely.

Despite the deleterious effects of age on the brain and behavior, increasing research has shown that the neural plastic potential is preserved until late adulthood (e.g., [27]). Cabeza [28] found that high-performing older adults could counteract age-associated neural decline by recruiting bilateral prefrontal regions when performing a cognitively demanding source memory task, as opposed to the right lateralization observed in both younger adults and low-performing older adults. The reduction in hemispheric asymmetry appears to compensate for the age-associated decline in cognitive performance by reorganizing the neural recruitment [28, 29]. In another study, Boyke et al. [30] found that older adults demonstrated a similar extent of gray matter changes in the middle temporal area of the visual cortex (hMT/V5) as did their younger counterparts, after acquiring the skill of juggling a three-ball cascade. Although the juggling performance of older adults was less proficient than that of their younger counterparts, the observed brain structural changes in the visuomotor region bolstered up the claim that an aging brain is still capable of change in response to experience. Further support was substantiated by Colcombe et al. [31], which showed that older adults demonstrated significant increases in brain structural volume after completing aerobic exercise training, in comparison to that of the older adults in the stretching control group.

Considering that our brain retains its neural plastic potential until late adulthood, lately there has been a growing trend toward exploring any cost-effective intervention that can mitigate or even slow down the age-related declines in cognitive functions. Such cognitive training or interventions are primarily targeted at training either general cognitive function or specific cognitive domains, such as attention and working memory, and promising findings have been received thus far (e.g., [32–35]). Building on the principle of neuroplasticity and the concept of the sensory deprivation model, Smith et al. [36] developed a self-administered cognitive training program that aimed at improving the auditory processing speed as well as its accuracy. Their program consists of six computerized exercises that stress sharpening one's ability to discriminate, judge, recognize, and match the sequences or pairs of confusable syllables; to reconstruct the sequences of verbal instruction; and to discern the details after listening to a story presented verbally. Individuals are encouraged to perform cognitive exercises for one hour every day, five days per week, for a total of eight weeks (equivalent to 40 sessions). It was found that participants demonstrated significantly greater improvement in auditory attention and memory after completing the Brain Fitness Program, when compared with their peers in the Active Control Group [36].

Recently, the feasibility and potential of implementing the cognitive training program to older adults at risk of cognitive decline have garnered increasing empirical attention and equivocal evidence has been obtained (e.g., [37, 38]). It is important to gather evidence on whether the cognitive training can induce general or specific neural plastic changes in cognitive function among the older adults who experience greater than normal rate of age-related cognitive decline and predispose to greater risk of developing dementia or specifically AD (e.g., [39, 40]). To bridge the aforementioned research gap, the current study was a longitudinal study that examined the specific cognitive effects of planned experience delivered in a cognitive training program. The program, modeled after the Brain Fitness Program [36], aimed at providing the training for attention and working memory but not verbal or visual-spatial memory of older adults at risk of cognitive decline. Based on the principle of experience-induced neural plasticity, it is hypothesized that participants from the Cognitive Training (CT) Group, relative to their peers in the Active Control (AC) Group, would demonstrate training-specific improvement in attention and working

memory but not verbal and visual-spatial memory following 13 weeks of cognitive training.

## 2. Method

*2.1. Participants.* Ethics approval of this study was granted by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB). Informed consents for participation in this study were obtained from the 209 right-handed community-dwelling Chinese older adults at risk of cognitive decline recruited via a local monthly newsletter, local elderly centers, and word of mouth. These older adults were considered at risk of cognitive decline because their Montreal Cognitive Assessment (MoCA) scores fell into the range of 19 to 26 [41]. Other than meeting the MoCA's cutoff score, the participants also fulfilled the following inclusion criteria: they (1) were 60 years old or above, (2) were literate, (3) had normal or corrected-to-normal vision and/or hearing, (4) were right-hand dominant as assessed by the Lateral Dominance Test [42], and (5) had normal intelligence as measured by the Test of Nonverbal Intelligence (TONI-III) [43]. Participants were excluded from this study if they met one of the criteria below: they (1) had current or a history of neurological or psychological disorders (e.g., head injuries, stroke, major depression, or generalized anxiety disorder), (2) had current or a history of substance abuse and/or alcoholism, (3) were on antidementia medication and/or (4) were diagnosed with thyroid dysfunction or vitamin B12 deficiency, and (5) scored in the moderate or severe range (≥11) in either subscales (depression or anxiety) of Hospital Anxiety and Depression Scale (HADS) [44].

The 209 participants were randomly assigned to the CT and AC groups by an experimenter blind to the cognitive status of the participants using computer-generated random sequences of numbers. Specifically, each participant ID was paired with a random number and the order of the participants was rearranged based on the value of the assigned number (from smallest to largest). Results of Significance Test confirmed that the CT and AC groups did not differ in demographic characteristics, cognitive processing speed, and depression scores, variables that have been consistently reported to play a significant role in modulating the rate of cognitive decline (e.g., [45–48]).

*2.2. Cognitive Training: Training Protocol.* The training protocol used in this study was modelled after the Brain Fitness Program (Posit Science, San Francisco, California, Glenn Smith). It is a self-administered training program of three one-hour sessions per week for a total of thirteen weeks. Older participants in the CT group were encouraged to practice four out of six cognitive exercises (approximately 15 minutes each) in each training session. In the following, a brief description of each of the six cognitive exercises was provided.

*2.2.1. Sound Sweeps.* In each trial, participants are presented with two sound sweeps. Each sound sweep either begins low and rises upward or begins high and goes downward. Participants are instructed to indicate the frequency of the two sound sweeps by clicking the corresponding arrows using the mouse. For example, up-arrow "↑↑" represents that the frequency of the sound sweep shifts from low to high, whereas the down-arrow "↓↓" means that the frequency of the sound sweep shifts from high to low. Participants have to respond as quickly and accurately as they can. Their reaction times and response accuracy for each trial are recorded.

*2.2.2. Size Discrimination.* In this exercise, participants will be presented with two orange heptagons in each trial. Their task is to discriminate between the different sizes of the heptagons and to identify which heptagon (left or right) has a relatively larger size. To increase the level of difficulty, the size contrast decreases (i.e., the size difference is not that apparent) as the number of trials advances. Their reaction time and response accuracy for each trial are recorded.

*2.2.3. Matching Pairs of Syllables.* In each trial, eight cards are shown on a screen. Each card is associated with a syllable. Whenever the participants click on each card, they hear a specific sound (syllable). Their task is to pair up the same syllables that are randomly dispersed among the eight cards. Participants can hear the sound as many times as they can but they are encouraged to complete the matching task using the minimal number of steps. Their reaction times and response accuracy for each trial are recorded.

*2.2.4. Matching Pairs of Rhythm.* In each trial, participants hear two pairs of rhythm and are asked to recognize whether the two pairs of rhythm are the "same" or "different." The level of difficulty increases with increased length of the rhythm. The participants' reaction times and response accuracy for each trial are recorded.

*2.2.5. Chasing the Stars.* In this exercise, participants are first shown three stars appearing in random locations on the screen in quick succession. Their task is to repeat the sequence and location where the three stars were shown on the screen in the same order. If the participants' performance reaches a certain level of accuracy, they would proceed with "four-star" and "five-star" conditions. Their reaction times and response accuracy for each trial are recorded.

*2.2.6. Narrative Stories.* Participants are instructed to listen to a number of short narrative stories that comprise short conversations and answer the questions pertaining to the details of the conversation afterward.

*2.3. Active Control.* The purpose of the AC group was to ascertain whether the observed improvement in cognitive functioning can be attributed to factors (e.g., the training format) other than the training content. To account for the confounding factors, the training duration, frequency, and format of the AC group were comparable to those of the CT group, except the content of the training. Participants in the AC group did not work on the same kinds of cognitive

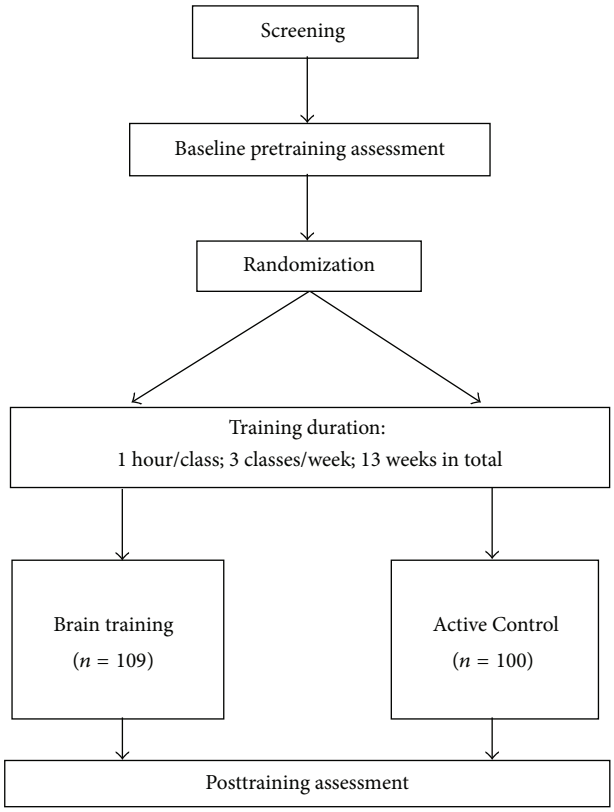


Figure 1: Flowchart of the longitudinal study of the thirteen-week cognitive training program.

exercises as did their peers in the CT group. Instead, they were shown educational programs covering diverse topics (e.g., history, science, health information, and local social issues) on a group basis. Immediately after watching the video, they were instructed to answer several questions that were related to the video content.

*2.4. Study Design and Procedure.* The current study adopted a longitudinal study design to evaluate the effects of a brain plasticity-based training program on enhancing attention and working memory in a group of Chinese older adults at risk of cognitive decline (Figure 1). All participants from the CT and AC groups were required to attend a total of 39 one-hour training sessions over thirteen weeks in groups of four to eight. For both the CT and AC groups, each participant was assigned a laptop, a headset, and a mouse that were used for performing the cognitive exercises. They used the same laptop for their entire training. All the training sessions were conducted in a quiet and well-lit room in our laboratory. A research assistant was present in each training session to keep track of their attendance and address any questions pertaining to the task instruction raised by the participants. These research assistants were also responsible for conducting the posttraining assessments.

*2.5. Outcome Measures.* To capture training-associated changes in cognitive function, several cognitive measures on sustained attention, working memory, and memory were administered to all the older adults before and after completing the cognitive training.

*2.5.1. Sustained Attention.* The Digit Vigilance Test is a measure of vigilance and sustained attention that requires participants to cross out a target number, as fast as they can, throughout the page of digits mixed with other numbers. The numbers are randomly dispersed throughout the page, which adds to the difficulty of identifying the target numbers. Both the reaction time and number of errors are recorded. In our study, only the reaction time was included for statistical analysis. The Seashore Rhythm Test taps an individual's ability to discriminate between "similar" and "dissimilar" pairs of rhythms and demands auditory attention. Participants listen to one pair of musical beats at a time and are asked to judge whether each pair of musical beats is "similar" or "different" right after its presentation. A total of 30 pairs of rhythmic beats will be administered. The total number of accurately identified items is recorded.

*2.5.2. Working Memory.* The Digit Span Test of the Wechsler Memory Scale, Third Edition (WMS-III), is a measure of auditory working memory. Subjects are instructed to repeat the strings of digits in the same (forward sequence) and reverse (backward sequence) order that is verbally presented by the examiner. The level of difficulty increases as the length of the string of the digits increases. The WMS-III Visual-Spatial Span Test assesses the visual-spatial working memory and requires the subjects to touch or point at the blocks in the same (forward sequence) and reverse (backward sequence) sequences as demonstrated by the examiner.

*2.5.3. Memory.* The Logical Memory Subtests of the WMS-III were used to measure verbal memory. Subjects are required to recall two stories that are verbally presented by the examiner immediately and after a delay. Following the delayed recall trials, a forced-choice "Yes/No" recognition test is also administered. The Family Pictures Subtest of the WMS-III measures visual-spatial memory. The participants were shown four pictures, one at a time, and were asked to recall the details of each picture.

*2.6. Statistical Analysis.* Prior to the statistical analyses, an independent $t$-test was conducted to examine if any between-group differences (CT and AC) in the demographic variables (age, gender composition, and levels of education), general intellectual abilities (scores on TONI-III), cognitive processing speed (processing speed index on the Wechsler Adult Intelligence Scale, Third Edition (Chinese version)), cognitive status (scores on the Cantonese version of MoCA), and depression (scores on the Geriatric Depression Scale) were present.

A 2 (Training Groups: CT and AC) × 2 (Time-Points: Pretraining and Posttraining) Repeated Measures ANOVA was used to examine the training effect on sustained attention, working memory, and memory, in Chinese older adults at risk

Table 1: Comparison between the Cognitive Training and Active Control Groups on their demographic characteristics, cognitive processing speed, and depression scores at baseline.

| Variables | Cognitive Training ($n$ = 109) M (SD) | Active Control ($n$ = 100) M (SD) | Test of group differences $P$ value |
|---|---|---|---|
| Age (years) | 70.1 (6.21) | 70.0 (6.60) | .953 |
| Years of education | 8.71 (3.84) | 9.49 (4.44) | .173 |
| Gender composition | 87 F : 22 M | 77 F : 23 M | .736 |
| TONI-III | 16.6 (5.34) | 17.7 (6.64) | .218 |
| MoCA | 23.6 (1.88) | 23.8 (1.97) | .494 |
| WAIS-III PSI | 71.0 (22.40) | 72.3 (22.74) | .677 |
| GDS | 4.61 (2.67) | 4.31 (2.41) | .403 |

Note: only the demographic characteristics of the Cognitive Training and Active Control Groups were listed here. TONI-III = Test of Nonverbal Intelligence (Third Edition) (total raw score); MoCA = Montreal Cognitive Assessment, Hong Kong version (Total Score); WAIS-III PSI = Wechsler Adult Intelligence Scale, Third Edition Processing Speed Index (cumulative raw scores of the Digit-Symbol Coding subtest and Symbol Search subtest); GDS = Geriatric Depression Scale; level of significance: $P < .05$.

of cognitive decline. Post hoc comparisons (paired sample $t$-tests) were carried out for each significant interaction effect to further clarify the effect of cognitive training on a specific outcome measure.

## 3. Results

*3.1. Participants' Characteristics.* Our final sample consisted of 209 older adults aged 60 to 88 years (164 females and 45 males; age: M = 70.1 years; SD = 6.38 years) who successfully completed the pre- and posttraining assessment, of which 109 older adults were randomly assigned to the CT group (87 females and 22 males; age: M = 70.1 years; SD = 6.21 years) and 100 older adults were in the AC group (77 females and 23 males; age: M = 70.0 years; SD = 6.60 years) (Table 1).

Participants from the CT and AC groups were matched for their demographic characteristics (age, gender composition, and years of education), cognitive processing speed, and depression scores (all $P > .05$).

*3.2. Training-Associated Changes in Cognitive Functioning*

*3.2.1. Sustained Attention.* Seashore Rhythm Test and Digit Vigilance Test are the indicators of the auditory and visual attention. A 2 (Training Groups: CT and AC) × 2 (Time-Points: Pre- and Posttraining) Repeated Measures ANOVA only revealed significant interaction effect on the Seashore Rhythm Test, $F(1, 207) = 5.054$, $P = .026$, but not on the reaction time of the Digit Vigilance Test, $F(1, 207) = .046$, $P = .831$ (Table 2). Post hoc comparison indicated that only the CT group demonstrated significant improvement in the Seashore Rhythm Test following the training, $t(108) = -3.707$, $P < .000$, whereas the AC group did not show any significant change in their scores but simply maintained a similar level of performance on the Seashore Rhythm Test upon completion of the training, $t(99) = -.796$, $P = .428$.

*3.2.2. Working Memory.* Digit and Visual-Spatial Span assess the verbal and visual-spatial attention and working memory, respectively. The two-way Repeated Measures ANOVA only identified significant interaction effects on the Total Digit Span, $F(1, 207) = 6.473$, $P = .012$, as well as the Total Visual-Spatial Span, $F(1, 207) = 5.047$, $P = .026$, which represent auditory and visual-spatial attention and working memory (Table 2).

Post hoc comparisons showed that the CT group exhibited significant increases in the Total Digit Span, $t(108) = -4.119$, $P = .000$, and Total Visual-Spatial Span, $t(108) = -3.835$, $P = .000$, after three months of cognitive training. In contrast, the AC group did not show any statistically significant increase or decrease in the Total Digit Span, $t(99) = -.121$, $P = .904$, and Total Visual-Spatial Span, $t(99) = -.552$, $P = .582$.

*3.2.3. Memory (Immediate and Delayed Recall).* Both immediate and delayed recall trials of WMS-III subtests of Logical Memory and Family Picture were chosen to examine the training effect on auditory and verbal memory, respectively. Neither the main effects nor interaction effects on the immediate and delayed recall trials of WMS-III Logical Memory and Family Picture were significant (all $P > .05$) (Table 2).

*3.3. Correlation between Cognitive Status and Training Effect.* To explore whether levels of cognitive status would have been associated with different training outcomes, Pearson correlational analyses were carried out between the baseline general cognitive statuses (as measured by MoCA) and the pre- versus posttraining changes in cognitive measures among the older participants from the CT group. None of the pre- versus posttraining changes in cognitive variables (including attention, working memory, and cognitive processing speed) was significantly correlated with the initial general cognitive statuses of the participants from the CT group (all $P > .05$).

## 4. Discussion

This study used a longitudinal design to examine the specific effect of planned experience on cognitive functioning. Consistent with our *a priori* hypothesis, behavioral changes are specific to the types of experience induced to the brain. In

Table 2: Results from the 2 (Training Groups: Cognitive Training and Active Control) × 2 (Time: Pre- and Posttraining) Repeated Measures ANOVA.

| Cognitive domain | Raw scores | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cognitive Training ($n$ = 109) | | | | Active Control ($n$ = 100) | | | | Repeated-Measures ANOVA for Training Group-by-Time Interaction | |
| | Baseline | | After 13 weeks of training | | Baseline | | After 13 weeks of training | | | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | $F$ (df = 1, 207) | $P$ value |
| Sustained attention | | | | | | | | | | |
| Digit Vigilance Test | 492.53 | 152.51 | 460.53 | 123.93 | 482.38 | 114.23 | 447.13 | 116.58 | .046 | .831 |
| Seashore Rhythm Test | **19.80** | **3.84** | **21.13** | **3.70** | **20.73** | **3.60** | **20.98** | **3.57** | **5.054** | **.026*** |
| Working memory | | | | | | | | | | |
| Digit Span | | | | | | | | | | |
| Total | **19.16** | **3.77** | **20.00** | **3.64** | **19.99** | **3.95** | **20.02** | **4.41** | **6.473** | **.012*** |
| Visual Spatial Span | | | | | | | | | | |
| Total | **13.11** | **3.06** | **14.04** | **2.91** | **13.44** | **2.97** | **13.58** | **2.91** | **5.047** | **.026*** |
| Memory | | | | | | | | | | |
| WMS-III Logical Memory | | | | | | | | | | |
| Immediate recall | 26.21 | 10.43 | 30.31 | 10.68 | 27.14 | 9.64 | 32.26 | 10.88 | .933 | .335 |
| Delayed recall | 14.81 | 7.46 | 18.24 | 7.73 | 15.56 | 7.25 | 19.75 | 8.37 | .913 | .340 |
| WMS-III Family Pictures | | | | | | | | | | |
| Immediate recall | 27.39 | 10.96 | 29.20 | 10.57 | 27.18 | 11.24 | 29.19 | 11.60 | .027 | .869 |
| Delayed recall | 27.17 | 10.66 | 28.57 | 10.17 | 26.04 | 11.77 | 27.81 | 11.94 | .089 | .765 |

Level of significance: $^*P < .05$.

this study, only attention and working memory, but not verbal and visual-spatial memory, showed an improvement after the 13-week systematic cognitive training of these cognitive domains. This pattern of finding is consistent with the prediction set forth by experience-dependent neural plasticity model. The specific improvement in attention and working memory cannot be attributed to other demographic, cognitive, or emotional variables because the CT and AC groups were matched on these dimensions. These training-induced modality-specific improvements in attention and working memory performance have underscored the importance of designing a tailor-made experience as to induce experience-specific changes in cognitive functions (e.g., [2–7, 49, 50]). Perhaps future research can consider exploring the potential of cognitive intervention that is targeted at training a specific cognitive domain or even a specific modality. For example, it is well-documented that atrophy of the medial temporal lobe (especially in the hippocampus) may explain the aging-related memory impairment [24–26]. Based on the findings of this study, planned cognitive training inducing learning and memory consolidation may lead to experience-specific neural plastic changes in the hippocampus leading to long-term memory enhancement. Furthermore, while memory is the major cognitive domain being affected in people suffering from Alzheimer's disease, training targeted at verbal and visual-spatial memory may be beneficial in slowing the memory decline.

The nonsignificant training effect on sustained attention, measured by the Digit Vigilance Test, is inconsistent with previous findings [36]. We speculated that the discrepant findings could relate to the use of different age cohorts between ours and previous studies. Literature has pointed out that normal aging is associated with widespread neuronal and synaptic atrophy [12] and physiological degradation [51], which contribute to age-related blunting of neuroplastic responses in an aging brain [49].

On the CT group, our correlational analyses showed that their initial general cognitive status was not significantly associated with any of the pre- versus posttraining changes in cognitive variables of interests (including attention, working memory, and memory), indicating that older adults who were considered to be at greater risk of cognitive decline could capitalize on the cognitive training to a similar extent and their initial cognitive status may not confine the neural plastic potential of their aging brains. Considering that our study specifically targeted older adults who scored within the restricted range of MoCA (i.e., 19 to 26), it remains unclear whether the significant correlation identified in our study can be generalized to the elderly population who scored in the normal range, so it is worthwhile to look into this unaddressed question in the future.

The findings of this study could be complemented by neuroimaging data that can inform the neural changes associated with the observed behavioral improvement. Future research could investigate whether cognitive training can trigger changes at both the behavioral and neural levels, which could definitely advance our understanding of the mechanisms underlying the training effects. Future studies can probe into the temporal window during which the transition from the neural plastic changes to behavioral changes can be captured. Previous reports have suggested the importance of understanding the generalization of the training effect to activities of daily living (ADL) [52] and other untrained cognitive domains [53]. Unfortunately, we were unable to test for the generalization of the training effects beyond the laboratory setting. It is worthwhile to devote the research effort to elucidate the mechanism underlying the training-transfer effects in order to augment the beneficial effect of cognitive training brought to older adults. While the current study did not intend to inspect the potential impact of educational background on the training effect and hence matched for older participants' level of education, our previous study did report that the less educated older adults were more likely to gain from the cognitive training than their better educated peers [54]. Future investigation can gauge the potential role of educational background and possibly other factors as to maximize the extent to which the older adults can take advantage of the cognitive training.

## 5. Conclusion

The aging of populations is a pressing issue worldwide. Cortical degeneration accompanied by aging, coupled with cognitive deterioration, has placed a heavy socioeconomic burden on the health care system. Increasing research has evidenced that our brain retains a capacity to change in response to experience until late adulthood. Our findings shed insight into the potential of implementing cognitive training for older adults at risk of cognitive decline and provided substantial support that the neural plastic potential continues until older age. Most importantly, this study has provided strong evidence for the potential application of the experience-induced neuroplasticity model to develop cost-effective strategies that can potentially slow down the rate of cognitive decline associated with aging.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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*Clinical Study*

# Restoration of Central Programmed Movement Pattern by Temporal Electrical Stimulation-Assisted Training in Patients with Spinal Cerebellar Atrophy

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Disrupted triphasic electromyography (EMG) patterns of agonist and antagonist muscle pairs during fast goal-directed movements have been found in patients with hypermetria. Since peripheral electrical stimulation (ES) and motor training may modulate motor cortical excitability through plasticity mechanisms, we aimed to investigate whether temporal ES-assisted movement training could influence premovement cortical excitability and alleviate hypermetria in patients with spinal cerebellar ataxia (SCA). The EMG of the agonist extensor carpi radialis muscle and antagonist flexor carpi radialis muscle, premovement motor evoked potentials (MEPs) of the flexor carpi radialis muscle, and the constant and variable errors of movements were assessed before and after 4 weeks of ES-assisted fast goal-directed wrist extension training in the training group and of general health education in the control group. After training, the premovement MEPs of the antagonist muscle were facilitated at 50 ms before the onset of movement. In addition, the EMG onset latency of the antagonist muscle shifted earlier and the constant error decreased significantly. In summary, temporal ES-assisted training alleviated hypermetria by restoring antagonist premovement and temporal triphasic EMG patterns in SCA patients. This technique may be applied to treat hypermetria in cerebellar disorders. (This trial is registered with NCT01983670.)

## 1. Introduction

The cerebellum has long been known to be a key structure in the integration of descending motor command and ascending sensory feedback which account for the fluency and coordination of movements [1]. In cerebellar degenerative diseases such as spinal cerebral ataxia (SCA), the interlinked neural network is interrupted causing abnormalities in the excitation of targeted neurons which further worsen motor performance. An increasing number of associated genetic mutations have been identified in the past decade [2], of which SCA3 is the most prevalent, comprising about 1/3 of the general population [3]. At present, no known medical treatment can cure SCA.

The clinical symptoms of SCA include progressive ataxia, dysmetria, visual nystagmus, parkinsonism, muscular atrophy, spasticity, dysarthria, and hypotone [3]. Among these symptoms, hypermetria in patients with dysmetria is manifested as overshooting a predetermined target in limb movement [4–6]. Therefore, fast goal-directed movements such

Table 1: Basic data of the participants.

| | Groups | | $P$ |
|---|---|---|---|
| | Training | Control | |
| Number | 10 | 10 | — |
| Age (years) | 47 ± 8 | 51 ± 9 | 0.34 |
| Gender (F/M) | 8/2 | 5/5 | — |
| Onset duration (ms) | 8.60 ± 6.16 | 10.20 ± 2.36 | 0.48 |
| | Type III SCA ($n$ = 4) | Type III SCA ($n$ = 6) | |
| | Type VI SCA ($n$ = 2) | Unidentified ($n$ = 4) | |
| | Unidentified ($n$ = 4) | | |
| Finger-to-nose (times per 15 sec) | 11.2 ± 2.5 | 10.7 ± 2.4 | 0.66 |
| AG1-ANT latency (ms) | 88.84 ± 24.34 | 81.55 ± 31.12 | 0.57 |
| CE (%) | 13.43 ± 3.81 | 15.93 ± 6.39 | 0.3 |
| VE (%) | 3.91 ± 1.37 | 4.49 ± 2.05 | 0.46 |

as in the finger-nose-finger test are used to examine limb coordination movements in these patients. In hypermetria, motor sequences are usually characterized by abnormal timing with delayed muscle activation and sudden interruptions of movements followed by exaggerated corrections [7, 8]. These aberrations in both timing and coordination are often due to inadequate control of agonist and antagonist muscles [7, 8].

Healthy adults present with a specific triphasic electromyography (EMG) pattern when executing a fast goal-directed movement [9]. In the first phase, an agonist burst (AG1) initiates and accelerates the movement toward the target. In the second phase, antagonist activation (ANT) halts the movement at the exact target. A second agonist burst (AG2) in the third phase then reduces the effect of ANT to accurately place the limb at the predetermined endpoint of movement. In SCA patients, the triphasic EMG pattern is abnormal and shows a delayed onset of ANT [4, 10–13]. Several studies have suggested that the triphasic EMG pattern is centrally programmed [14, 15] in a feedforward mode independent of any sensory feedback [14, 16], with the cerebellum involved in the regulation of cortical premovement activity [17]. Transcranial magnetic stimulation (TMS) has shown that motor evoked potentials (MEPs) of agonist muscles are facilitated around 70–100 ms before the onset of movement, which is also known as premovement facilitation [15, 18, 19]. Our recent study on the preactivation of slow and fast goal-directed wrist movements showed a delay between the peaks of premovement facilitated MEPs in the agonist and antagonist muscles and that the delay was well correlated with the time course of triphasic EMG activation [20]. Therefore, abnormal premovement facilitation may be an important mechanism underlying hypermetria. Interventions which can modulate premovement facilitation may therefore be useful in improving hypermetria.

Fast goal-directed movement training has been shown to enhance cortical excitability [21, 22]. In addition, ES (electrical stimulation) of the afferent nerve has been shown to enhance cortical excitability through plasticity-like mechanisms in healthy subjects and in SCA patients [23–26]. These findings raised the possibility that combining temporal electrical afferent nerve stimulation and voluntary movement training may enhance premovement facilitation and improve the triphasic EMG pattern of movement. We therefore designed a temporal ES-assisted fast goal-directed movement training program for patients with SCA, under the hypothesis that such a training program could improve the temporal pattern of antagonist premovement facilitation, triphasic EMG pattern, and hypermetria in individuals with SCA. To the best of our knowledge, no clinical studies have focused on the temporal control of cortical excitability, especially in the premovement phase.

## 2. Methods

The study subjects were recruited from the Taiwan Spinocerebellar Ataxia Association after responding to advertisements. All of the study participants had been diagnosed with SCA (Table 1). The inclusion criteria were showing hypermetria during the finger-to-nose test, being able to sit independently to complete the experiment, no previous history of neuromusculoskeletal diseases other than SCA, and no severe tremors that would influence the recording of MEPs. Twenty-two subjects were screened, of whom 20 (age: 49 ± 8.43 years, 7 males, 13 females) met the inclusion criteria (Figure 1). The minimal sample size, which was estimated according to the data published in a previous study [20] (alpha = 0.05, power = 0.95), was 18. All of the study subjects provided informed consent, and the testing protocols were approved by our internal review board in accordance with the Helsinki Declaration. All clinical tests were performed by a licensed physical therapist who was blinded to group allocation. In addition, the subjects were also blinded to the purpose of this study.

*2.1. Electromyography Recording.* The experimental setup is shown in Figure 1. The right hand of each subject was used for the test, during which it was strapped to a custom-designed wrist goal-directed movement test and training system. The system included a laser pointer to show the wrist extension angle and a target line for 30° wrist extension. As the subjects performed the wrist movement, the laser pointer showed

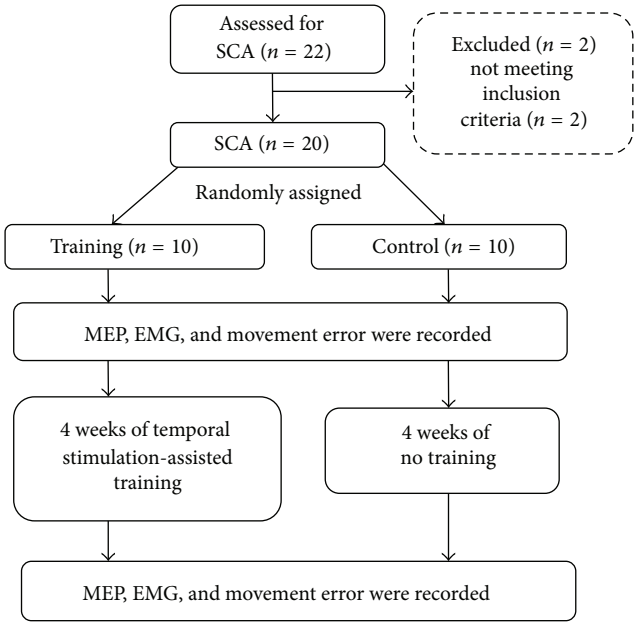


Figure 1: The flowchart of the study.

the movement angle in real time and provided visual feedback for the subjects. The forearm was kept neutral (0° supination) with the elbow at 80° flexion and the shoulder at 10° flexion.

The surface electromyography (EMG) of the flexor carpi radialis muscle (FCR) and the extensor carpi radialis muscle (ECR) was recorded by bipolar surface electrodes with a fixed interelectrode distance of 2 cm (B&L Engineering, Canada). The recording electrodes were located on the muscle belly of the FCR and ECR, with the direction parallel to the muscle fibers. A reference electrode was placed on the styloid process. The EMG activity was preamplified by a factor of 350 and further amplified at the mainframe amplifier (Gould Inc., Valley View, OH, USA). The raw EMG data were fed through a 60 Hz notch filter and a band-pass (10–1000 Hz) filter to eliminate environmental interference and motion artifacts. EMG activity was monitored on an oscilloscope and digitized by a 12-bit resolution analog-to-digital converter (InstruNet Model 100, Input/Output A/D System, USA) at 4000 Hz.

*2.2. Transcranial Magnetic Stimulation.* The MEPs of the FCR were elicited by the TMS (Magstim 200, Magstim Co., Dyfed, UK) using a round coil with a 9 cm outside diameter with an anticlockwise-oriented current in the coil (side A facing up) to stimulate the left motor cortex. The optimal scalp location that consistently produced the largest MEPs in the target muscle (FCR) at the lower intensity was marked, and this location was used throughout the experiment. The coil was manually maintained by a custom-designed fixation frame, and the position and orientation of the coil were kept constant throughout the experiment. The resting motor threshold was defined as the minimum TMS intensity required to elicit at least five of 10 MEPs greater than or equal to 50 $\mu$V in consecutive trials in the relaxed FCR [27, 28]. The stimulation intensity for the experiment was set at 20% above the resting motor threshold.

*2.3. Goal-Directed Movement Test.* After practicing several times, the subject's right arm was trapped in a custom-designed wrist goal-directed movement test and training system to perform five fast goal-directed wrist extensions. The system included two movable segments that were placed and fixed around the wrist. An electrogoniometer (SG75, Biometrics Ltd., UK) was mounted on these two segments to record the angle during movement. A laser light beam corresponding to the movement of the hand segment was projected onto a screen to provide the subjects with real-time visual feedback. The starting and target angles (30° of wrist extension) were measured and marked and constantly displayed on the screen. The subjects were instructed to perform the wrist extension as quickly as possible and to stop the movement when the laser pointer reached the targeted line indicating 30° of wrist extension. The EMG of the ECR (the agonist muscle) and FCR (the antagonist muscle) and joint angle were recorded for further analysis. The reaction time was also recorded for the following premovement MEP test.

*2.4. Premovement MEP Test.* An audio warning signal followed by an audio go-signal after 6–10 seconds was given through an earphone. The subjects were asked to perform the goal-directed movement test as mentioned above as soon as the go-signal was heard. The MEPs were elicited by a single pulse TMS at different time intervals in 10 ms steps after the go-signal. We wrote four sets of controlling programs, the most suitable of which were selected to assess the MEPs according to the subject's reaction time to ensure that the premovement MEPs were obtained at least 120 ms before the onset of movement (Table 2). After the assessment, the MEPs were grouped according to the onset of the agonist muscle (ECR) EMG into bins of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, and 120 ms before onset for analysis. Each of the intervals was repeated five times and delivered in a random order. Control MEPs were evoked by TMS without any audio signal (Figure 2).

*2.5. Temporal ES-Assisted Training.* After the pretest, the subjects in the training group received 4 weeks of temporal ES-assisted training at home at a training frequency of three sessions per week. During training, paired electrical stimuli were delivered every 15 seconds for 30 minutes through surface electrodes placed on the muscle bellies of the FCR and ECR. The intensity of the stimulus was set to the minimal intensity that would elicit a visible contraction of the stimulated muscle, and the pulse duration was set to 500 $\mu$s. Each stimulation pair included ECR stimulation followed by FCR stimulation with an interstimulus interval of 40 ms. The 40 ms interval was chosen because our previous study on healthy subjects showed an average of a 40 ms delay between AG1 and ANT (AG1-ANT latency) in goal-directed fast movements [20]. The subjects were asked to perform the 30° fast goal-directed wrist extension movement

Table 2: Stimulation protocol.

| Program | Reaction time of the subjects (ms) | Stimulation intervals (ms after the go-signal) |
|---|---|---|
| 1 | Less than 200 | 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220 |
| 2 | 180–250 | 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250 |
| 3 | 200–270 | 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270 |
| 4 | 240–310 | 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310 |

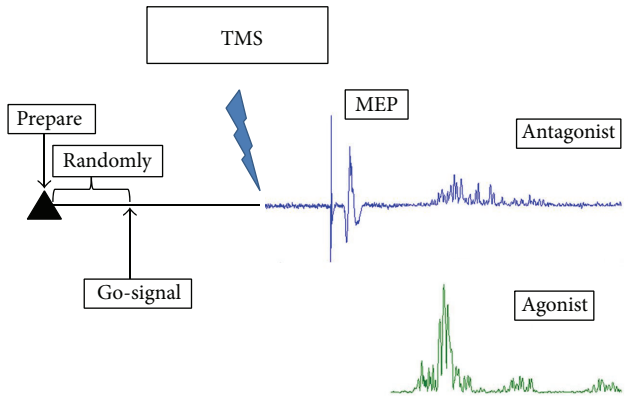


Figure 2: The procedure of the premovement MEP test.

immediately after perceiving stimulation of the ECR. The subjects in the control group received no training but some general health education. Goal-directed movement and premovement MEPs were assessed again after 4 weeks of training (training group) or in case of no training (control group), with these assessments being performed 3 days after the last training session.

*2.6. Data Analysis and Statistics.* The raw EMG data during the fast movement were transformed to the root-mean-square EMG (rmsEMG), and the onsets of ECR (AG1) and FCR (ANT) activation were calculated through rmsEMG-time curves. The onsets of ECR and FCR activation were detected when the curve passed through the threshold which was at the mean plus twice the standard deviation of the baseline. AG1-ANT latency was calculated by subtracting the ECR onset time relative to the FCR onset time and analyzed only in the trials with goal-directed movement tests without TMS or ES.

The peak-to-peak amplitude of the premovement MEPs at various time points before the onset of movement was normalized to the control MEPs. The normalized premovement MEPs were then averaged by predetermined time bins of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, and 120 ms, before the agonist muscle (ECR) EMG onset. The EMG onset of the ECR was determined for each subject in the trials without TMS in order to avoid the potential influence of TMS. The premovement MEPs elicited 130 ms before agonist muscle EMG onset were not analyzed. Linear interpolation was used to adjust the MEP amplitude if the MEPs were elicited between the aforementioned predetermined time bins.

The quality of performance was analyzed in the trials of the goal-directed movement test without TMS or ES. The final angles used to calculate the constant errors (CEs) and variable errors (VEs) were those at the end of the ballistic movement, measured before any corrective movements were made by the participant. The quality of performance was calculated using CEs and VEs. CEs, which measured the errors of goal setting, were calculated by the mean difference between the goal-directed angle and each actually performed angle (1) [29, 30]. VEs, which measured the inconsistency of repetitive measures, were calculated by the standard deviation of the difference between the goal-directed angle and each actually performed angle (2) [29, 30]. Consider

$$\mathrm{CE} = \frac{\sum (Xi - T)}{n}, \tag{1}$$

where $Xi$ is the angle at which the subject stopped, $T$ is the target angle, and $n$ is the number of movements;

$$\mathrm{VE} = \frac{\sqrt{\sum (Xi - M)^2}}{n}, \tag{2}$$

where $Xi$ is the angle at which the subject stopped, $M$ is the averaged angle, and $n$ is the number of movements.

Data were analyzed using SAS software version 9.1. Two-way repeated-measures analysis of variance (ANOVA) with factors of group (training and control) and time (before and 4 weeks after) followed by the post hoc Tukey test (when needed) was used to determine and compare the effect of training on premovement MEPs, VEs, and CEs. If a significant group and time interaction was found, the model was further reduced by group. The significance level was set at $P < 0.05$.

## 3. Results

There were no between-group differences in any of the measured parameters including CEs (hypermetria), AG1-ANT latencies, and MEP at baseline. The $P$ values of the baseline comparisons are listed in Table 1.

*3.1. EMG Pattern of Goal-Directed Movement Test.* ANOVA showed a significant interaction between groups and time

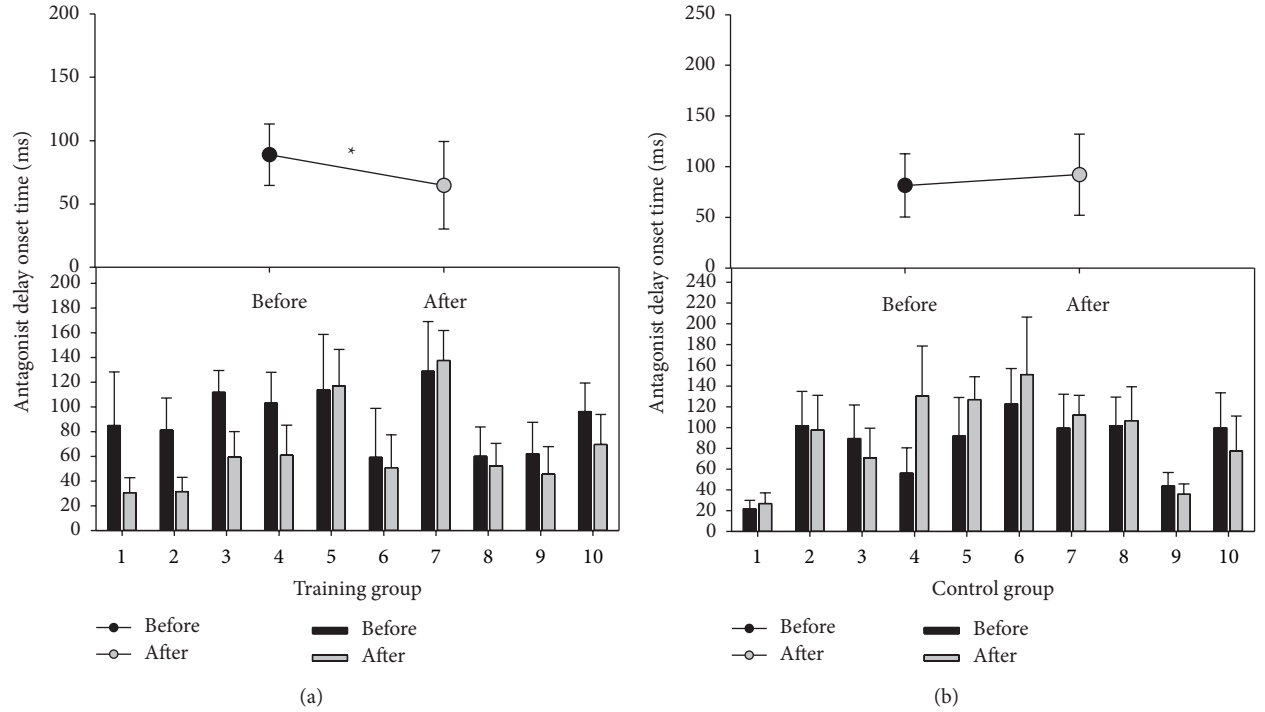


Figure 3: The latency of antagonist muscle activation (AG1-ANT latency) during fast goal-directed wrist extension movement in the training group (a) and the control group (b). The upper panel shows the group means and standard deviations. The lower panel shows the individual means and standard deviations. The black circle and bars indicate before training, and the gray circle and bars indicate after 4 weeks of training. $P > 0.05$ before and after 4 weeks.

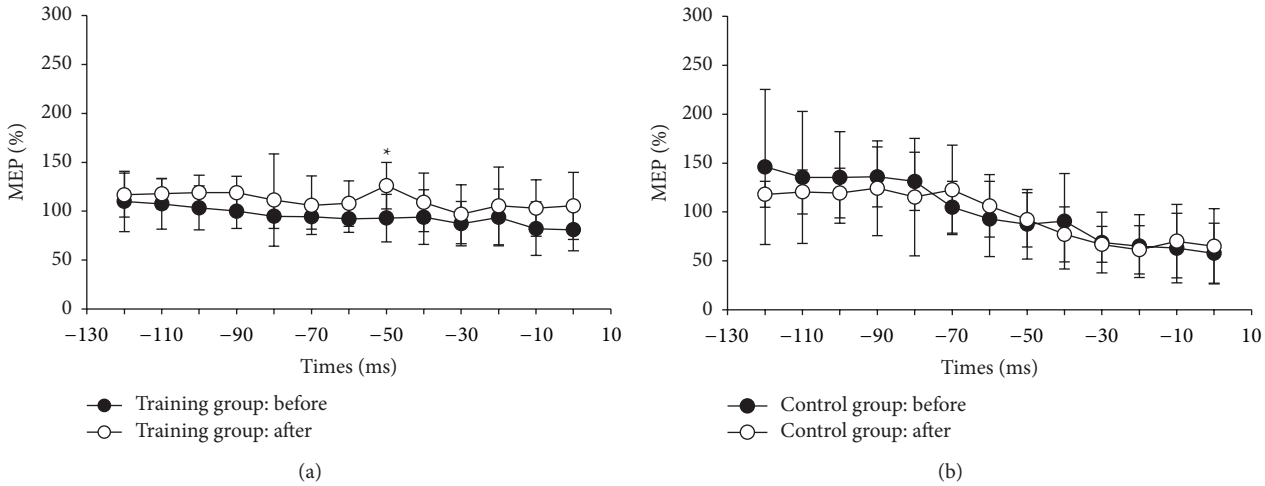


Figure 4: The normalized MEP amplitudes before onset latency of the antagonist muscle EMG of fast goal-directed wrist extension movement in the training group (a) and the control group (b). The black circles indicate the group mean before training, and the white circles indicate the group mean after the 4-week training program. The error bars indicate the standard deviations.

($F = 8.84$, $P = 0.008$). Before training, the AG1-ANT latencies were not significantly different between the training and control groups. However, after 4 weeks, the latency of antagonist muscle activation was significantly decreased to $64.66 \pm 34.56$ ms ($F = 10.65$, $P = 0.0098$) for the training group with no significant change in the control group ($F = 1.37$, $P = 0.2716$) (Figure 3).

*3.2. Premovement Facilitation.* Figure 4 shows the premovement MEPs before and after 4 weeks of training in the training and control groups. Before training, the premovement MEPs of the antagonist muscle were not facilitated in either the training or control group in the fast goal-directed wrist movements. A significant group and time interaction ($F = 5.4$, $P = 0.0336$) was found 50 ms before the onset of

Table 3: Group means ± standard deviation of premovement MEP, AG1-ANT latency, CE, and VE.

| Time | Groups | | | | Statistical analysis Group × time interaction | |
|---|---|---|---|---|---|---|
| | Training before | Training after | Control group before | Control group after | $F$ | $P$ |
| | | | MEP (% of control MEP) | | | |
| −120 | 110.0 ± 30.9 | 116.6 ± 22.5 | 149.0 ± 84.0 | 118.4 ± 14.1 | 1.38 | 0.26 |
| −110 | 107.5 ± 25.9 | 117.8 ± 15.5 | 136.9 ± 72.1 | 123.1 ± 22.6 | 1.25 | 0.28 |
| −100 | 103.4 ± 22.4 | 119.0 ± 17.7 | 134.9 ± 50.1 | 119.8 ± 27.1 | 3.87 | 0.07 |
| −90 | 99.9 ± 17.5 | 118.8 ± 16.7 | 133.9 ± 32.2 | 122.5 ± 51.4 | 3.33 | 0.09 |
| −80 | 94.8 ± 12.5 | 111.3 ± 47.2 | 130.8 ± 31.9 | 117.3 ± 63.8 | 2.15 | 0.16 |
| −70 | 94.3 ± 12.5 | 106.0 ± 29.9 | 102.6 ± 27.4 | 122.4 ± 48.9 | 0.14 | 0.71 |
| −60 | 92.1 ± 13.7 | 107.9 ± 23.2 | 91.0 ± 40.8 | 108.7 ± 33.1 | 0.02 | 0.89 |
| −50 | 93.0 ± 24.3 | 126.2 ± 23.8* | 89.2 ± 37.6 | 85.8 ± 21.8 | 5.4 | 0.03* |
| −40 | 93.8 ± 27.9 | 108.9 ± 29.9 | 91.5 ± 52.0 | 75.1 ± 29.3 | 2.17 | 0.16 |
| −30 | 87.2 ± 22.7 | 96.8 ± 30.2 | 65.9 ± 31.8 | 67.1 ± 19.4 | 0.22 | 0.65 |
| −20 | 93.6 ± 29.1 | 105.4 ± 39.8 | 61.8 ± 32.8 | 61.7 ± 26.4 | 0.33 | 0.57 |
| −10 | 82.0 ± 27.4 | 103.1 ± 28.9 | 61.8 ± 37.8 | 65.2 ± 36.9 | 0.96 | 0.34 |
| 0 | 81.1 ± 21.6 | 105.4 ± 34.2 | 56.9 ± 32.5 | 62.7 ± 40.5 | 0.77 | 0.39 |
| AG1-ANT latency (ms) | 88.9 ± 24.3 | 64.7 ± 34.6* | 81.6 ± 31.1 | 92.2 ± 40.1 | 10.65 | 0.01* |
| CE (%) | 13.4 ± 3.8 | 10.2 ± 3.5* | 15.9 ± 6.4 | 18.2 ± 5.0 | 5.99 | 0.02* |
| VE (%) | 3.9 ± 1.4 | 2.5 ± 0.7 | 4.5 ± 2.1 | 4.8 ± 1.6 | 3.27 | 0.09 |

∗ is significantly different from pretraining.

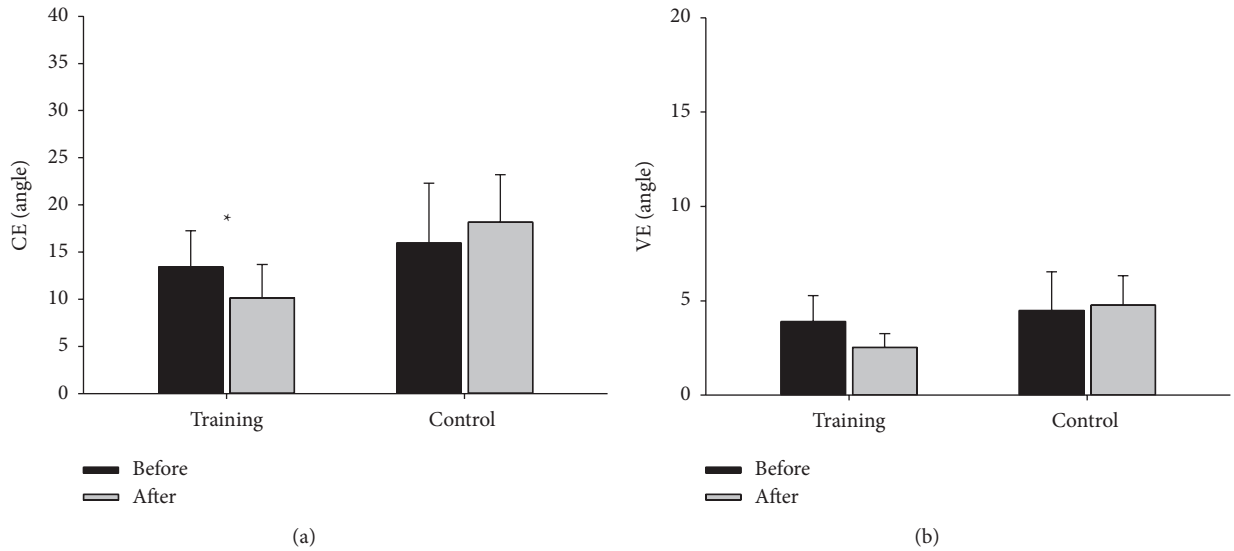


Figure 5: The group means and standard deviations of the CE (a) and the VE (b) of the training group (black bars) and the control group (gray bars) before and after 4 weeks.

movement (Table 3). In the training group, the premovement MEPs were significantly enhanced from 92.98 ± 24.31% to 126.16 ± 23.77% ($P < 0.05$) 50 ms before the onset of movement. However, the normalized MEPs did not change in the control group ($P > 0.05$).

*3.3. Performance.* Before training, there was no difference in CEs between the training and control group ($F = 1.123$, $P = 0.303$). Two-way ANOVA showed a significant group and time interaction ($F = 5.99$, $P = 0.0249$), with the CE decreased to 10.16 ± 3.53 degrees in the training group ($F = 6.43$, $P = 0.0319$) but unchanged in the control group ($F = 1.48$, $P = 0.2554$) (Figure 5(a)). Before training, the VEs were 3.91 ± 1.37 degrees and 4.49 ± 2.05 degrees in the training and control groups, respectively ($F = 0.565$, $P = 0.462$), compared to 2.52 ± 0.73 and 4.76 ± 1.56 degrees

after 4 weeks. Two-way ANOVA showed no significant group and time interaction ($F = 3.27$, $P = 0.0874$) (Figure 5(b)).

*3.4. Correlation Analysis.* Spearman correlation coefficient analysis showed a median but significantly negative correlation between AG1-ANT latency and antagonist MEP amplitude at 50 ms before the onset of movement ($r = -0.4066$, $P = 0.011$). This suggests that the increase in antagonist premovement facilitation was correlated with the decrease in AG1-ANT latency. However, no other correlations were found between the other parameters.

## 4. Discussion

In the present study, 4 weeks of temporal ES-assisted movement training decreased CEs, indicating an alleviation of hypermetria in the patients with SCA. In addition, the prolonged AG1-ANT latency was shortened toward the normal range, suggesting that the training corrected the aberrant triphasic EMG pattern in these patients. Furthermore, the premovement facilitation of the antagonist muscle, which was previously absent in the patients, was reestablished after the 4-week temporal ES-assisted training program.

Corcos et al. applied goal-directed movement only training for 200 repetitions per day for 7 days and showed only marginal improvement in accuracy in healthy subjects [31]. In the present study, we showed for the first time that a combination of temporal ES and movement training reduced CEs, which evaluate a subject's tendency to be directionally biased when performing a skill relating to the goal setting [29, 30], indicating that the coarseness of the movements in dysmetria was improved. We suggest that the effect of the temporal ES-assisted training program was through the synergistic effect of the ES and motor training. Repeatedly pairing stimulation with ES to the peripheral nerve and TMS to the motor cortex is commonly used to induce plasticity in the brain of conscious humans [32]. Hence, pairing ES and motor training may also induce a change in plasticity in the brain to enhance the training effect.

In the present study, the patients with SCA had a prolonged AG1-ANT latency compared to the healthy controls [20]. Activation of the antagonist muscle has been reported to change fast goal-directed movements [11, 33, 34]. The delayed onset of antagonist muscle activation can explain the hypermetria symptoms in patients with SCA. After 4 weeks of training, the AG1-ANT latency had significantly decreased, which may, at least in part, explain why the CEs improved, thereby resulting in better movement control by alleviating dysmetria. In healthy subjects, only an earlier peak of antagonist muscle EMG but no similar reduction in AG1-ANT latency has been shown after movement training [31, 35]. Instead, improvements in movement errors after pure movement training have been explained by increased recruitment rates of the antagonist muscle [35]. We suggest that further studies are warranted to investigate reductions in AG1-ANT latency.

We also found that the temporal ES-assisted training program partially restored premovement facilitation towards a normal pattern [20], although the significance of the facilitation at 50 ms before activation was marginal. The underlying mechanism remains to be elucidated. It is known that movement training can enhance excitability of the movement mapping cortical area [21, 22, 36], and it is generally considered to function through a long-term potentiation-like mechanism in which the horizontal synaptic connections in the brain cortex are enhanced through motor learning [22, 36–39]. Moreover, McDonnell and Ridding reported that subjects who received 1 hour of peripheral ES to the muscle responsible for movement prior to movement training had significant improvements in motor performance, suggesting that the peripheral ES enhanced motor performance and motor learning ability [40]. Peripheral ES has also been reported to facilitate the MEPs of the corresponding innervation muscles through plasticity-like mechanisms in various patients, including those with SCA [23–26].

Previous studies have indicated that the triphasic EMG pattern is centrally programmed [15, 41–43] and stored in the motor cortex [14, 17, 44]. The correlated enhancement of premovement facilitation and the reduction of AG1-ANT latency after temporal ES-assisted training in our study may support the centrally programmed theory of triphasic EMG pattern in ballistic movements. However, we failed to show other significant correlations between measurements, and it is possible that the relationship between the physiological improvements and functional improvements is complex and nonlinear.

Although VEs were slightly decreased after training, they did not reach a statistically significant difference, in contrast to the CEs. VE measures the inconsistency of performance [29, 30], and no significant improvement in VE suggests that the temporal ES-assisted fast goal-directed movement training did not improve the variability between each trial. The potential mechanism of the training effect in the present study is that the temporal ES-assisted training helped to rebuild the central program of the triphasic EMG pattern through changes in plasticity in the neural network. The fixed temporal pattern of ES that triggered the movement improved the accuracy of the muscle contraction pattern during the requested task resulting in better CEs. In contrast, the extension range of the training movement was not strictly controlled or trained, and it is therefore not surprising to see no improvements in VEs.

In the present study, we concentrated on the modulation effect of the temporal ES-assisted fast goal-directed movement training that improved the movement in the upper limbs functionally and physiologically in patients with SCA. However, it is unclear whether ES or movement training alone can achieve a similar or different effect. Therefore, further studies are warranted to explore the effect of ES or movement training alone and in combination. Another concern may be the relatively small subjects number (10 in each group) as compared to other physiological studies [45, 46]. This limitation is due to the difficulty of recruiting patients for a long-term training study. Hence, we cannot fully exclude the possibility of the error and the accuracy problem caused by the small sample size. Moreover, only single joint movement with fixed angle, stimulus intensity, and interval

was tested in the present study. Although the protocol was effective, it is not warranted to be the best.

In conclusion, 4 weeks of movement training guided by alternating temporal ES on the agonist and antagonist muscles shortened the latency between agonist and antagonist muscle activities, restored premovement facilitation, and improved movement accuracy in patients with SCA. Therefore, temporal ES-assisted fast goal-directed movement training can be considered to be a convenient and helpful therapeutic modality to improve hypermetria and may potentially be useful for patients with dysmetria caused by diseases including stroke, multiple sclerosis, multiple system atrophy type C, and other brain lesions.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## Acknowledgments

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*Research Article*

# Coincidence Anticipation Timing Performance during an Acute Bout of Brisk Walking in Older Adults: Effect of Stimulus Speed

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This study examined coincidence anticipation timing (CAT) performance at slow and fast stimulus speeds before, during, and after an acute bout of walking in adults aged 60–76 years. Results from a series of repeated measures ANOVAs indicated significant rest versus exercise × stimulus speed × time interactions for absolute and variable errors (both $P = 0.0001$) whereby absolute and variable error scores, when stimulus speed was slow, improved as the duration of exercise increased. When stimulus speed was fast there were significantly greater absolute and variable errors at 18 minutes of the walking bout. There was also greater error at 18 minutes during walking compared to rest. These results suggest that, in a task involving walking and CAT, stimulus speeds plays an important role; specifically walking (exercise) enhances CAT performance at slow stimulus speeds but reduces CAT performance at fast stimulus speeds. The implications are that in everyday situations, where events require dual-task responses to be made at different speeds, for example, walking on the pavement whilst avoiding a crowd, compared to crossing a busy road, an understanding of how different stimulus speeds influence dual-task performance is extremely important, particularly in the older adult population.

## 1. Introduction

In everyday life, irrespective of age, it is common that in a primary task such as walking the person will also engage in a secondary task involving some aspects of cognitive, perceptual, or motor control [1]. While walking is considered a more automated task in younger adults, it is already known that young adults adopt a slower walking speed under dual-task conditions [2]. Consequently, dual-task conditions pose an interesting paradigm for understanding the effect of walking (acute exercise) in older adults. Indeed, Woollacott and Shumway-Cook [3] postulated that walking becomes a less automated motor pattern with increasing age in adults over 60 years old as greater attentional resources are directed to ensuring gait is maintained.

Recent research has also suggested that in dual-task processing paradigms, where the primary task involves locomotion, performance of a secondary visual task is significantly impaired in older adults [1, 4, 5]. However, few studies have examined this empirically [6] with Beurskens and Bock [1] suggesting that when a visual secondary task is added to walking, the need to manage two streams of visual information concurrently (one related to walking and the other to the secondary task) exceeds the capability of an ageing prefrontal cortex resulting in a decrease in performance on one or both tasks.

Metaregression analysis [7] has identified that the effect of exercise on cognitive performance in adults is equivocal [8–13]. This is partly because most studies have examined cognitive performance on exercise cessation rather than during exercise whilst at the same time making conclusions regarding dual-task effects where exercise and cognitive performance are performed at the same time. In addition to the time of measurement, Lambourne and Tomporowski [7] identified that few studies have examined the effect of exercise on cognitive or perceptual performance in older adults. Therefore, it is particularly important to investigate the effect of exercise on secondary task performance in older adults as it has already been shown that there are age related decrease in brain mass, atrophy of the frontal gray matter, and

degradation of the cerebral cortex contributing to a reduction in cognitive processing capacity with advancing age [1].

The effect of exercise on cognitive performance is more likely to be of importance in older adults but is however poorly understood. One study that investigated the effects of exercise on cognitive performance in both young and older adults [14] asked participants to perform the Simon task, which is considered a test of executive function [14], whilst cycling (30 minutes at 65% of age predicted maximum heart rate). In the Simon task, participants are asked to respond as quickly and accurately as possible to a relevant feature of a stimulus (the colour) whilst inhibiting an irrelevant feature (the spatial location) of the same stimulus. Joyce et al. [14] noted that, although there were no differences in reaction time between older and younger adults, older adults adopted a more cautious approach to their task resulting in lower error rate compared to their younger peers. Other work by Barella et al. [15] investigated the duration of effects in cognitive performance (Stroop test) following 20-minute treadmill walking at an intensity of 60% heart rate reserve (HRR) in a sample of 40 adults aged 60–90 years. Barella et al. reported an immediate improvement in reaction time performance in the Stroop colour test immediately on exercise cessation but no other improvements or longer-term enhancement of cognitive performance.

One particular facet of cognitive performance, which is related to tasks of daily living, is coincidence anticipation timing (CAT). CAT is the ability to predict the arrival of a moving object at a particular point in space and coordinate a movement response with that arrival [16] and is strongly related to numerous tasks of daily living, particularly where predicting the arrival of a moving object is important, for example, crossing a busy street [17] or walking through a crowd while keeping an eye on another individual [5]. For example, when standing on the pavement of a busy street, the ability to predict when a car will reach (or pass) the place in the road where the pedestrian will cross is important. Likewise, when walking through a crowded street being able to "time" other individuals as they walk towards/around an individual is important in avoiding collisions or intercepting an individual (or moving object). It has been shown that older adults are negatively affected in tasks that have an element of CAT incorporated within them [18, 19] and that at rest the stimulus speed of the anticipation timing task (i.e., how fast the target or "stimulus" moves) may impact on CAT performance [20]. How exercise impacts on CAT and whether stimulus speed of the timing task impacts on any effect of exercise on CAT in older adults are yet to be established. This study sought to advance prior research by examining CAT performance at slow and fast stimulus speeds before, during, and after an acute bout of walking in older adults.

## 2. Materials and Methods

*2.1. Participants.* Following institutional ethics approval informed consent, 16 older adults (aged 60–76 years, age: 65.6±4.1 years, 7 females, 9 males) volunteered to participate. Descriptive data for the sample are presented in Table 1. All participants were habitually physically active (>150 min per week). Participants were excluded if they had any cardiovascular condition or were taking medications such as beta blockers or calcium ion channel blockers. Participants were asked to abstain from exercise for 24 hours prior to each visit and refrain from caffeine on waking each morning of the testing.

Table 1: Descriptive data.

| | Mean | SD |
|---|---|---|
| Age (years) | 65.6 | 4.1 |
| Height (m) | 1.68 | 0.07 |
| Body mass (kg) | 74.1 | 13.5 |

*2.2. Procedures.* The study used a repeated-measures design whereby participants undertook 3 visits to the laboratory. During the initial test session each participant was familiarised with the Bassin Anticipation Timer (Model 35575, Lafayette, USA) and given 20 attempts at each of the stimulus speeds used in the study (3 and 8 mph) to familiarise themselves with the test protocol. Resting heart rate (HRrest) was obtained from each participant whilst wearing a heart rate monitor (Polar RS400, Polar Electro Oy, Kempele, Finland), while they lay in a supine position for 10–15 minutes in a quiet room void of visual or auditory distractions. HRrest was recorded and used to calculate 50% age predicted HRR [6] to be used in the subsequent exercise trial. In the following two experimental trials, participants completed measures of CAT before, during, and immediately following a 20-minute passive rest condition or a 20-minute exercise condition. Each visit to the laboratory was separated by at least 72 hours and conditions were counterbalanced. For each condition, CAT measures were taken before, during: at 9 and 18 minutes, and after exercise.

*2.3. Exercise Condition.* In the exercise condition, participants were asked to walk on a treadmill (HP Cosmos Ltd., Germany) for 20 minutes at an intensity of 50% of HRR [6]. In the current study the threshold of 50% HRR was chosen as this is within the spectrum of exercise recommended by the ACSM for enhancement of cardiovascular fitness [21]. A 20-minute exercise duration was chosen as Lambourne and Tomporowski [7] identified this duration as most appropriate to identify any decrement in dual-task performance as a consequence of exercise. Heart rate was monitored throughout each trial. Borg's [22] rating of perceived exertion 6–20 (RPE) scale was used as an adjunct to the monitoring of heart rate. Participants were required to achieve an RPE of 13–15 during the exercise trial. An RPE of 13–15 is considered "light to moderate" intensity activity and commensurate with brisk walking. Walking speed was modified throughout to ensure that HRR remained at 50%, as has been the case in other studies [9, 13]. Walking speeds for the exercise condition, across all participants, were in the range of 4.4–6.5 km/h. This is congruent with reported speeds for "brisk" walking in older adults [23]. There was intratrial variation of approximately 0.5 km/h in walking speed to ensure each

Figure 1: Experimental setup of the Bassin Anticipation Timer. Arrow indicates location of the target light with the motion of the stimulus light moving from right to left.

participant remained at the required 50% HRR. At 9 minutes and 18 minutes during the exercise condition, participants performed 10 trials on the CAT task at each of the stimulus speeds of the timing task (3 and 8 mph) whilst still walking. The decision to assess CAT at 9 and 18 minutes during each condition was again based on the findings of prior metaregression analysis [7] showing different effect sizes for cognitive tasks performed from 0–10 minutes and 11–20 minutes during exercise. The rationale for the choice of stimulus speeds during the timing task was based on prior work with older adults which used stimulus speeds of 3 and 8 mph as indicative of "slow" and "fast" speeds [20].

*2.4. Rest Condition.* In the rest condition, participants were seated in a quiet room. At 9 minutes and 18 minutes during this condition participants performed 10 trials on the CAT task at each of the stimulus speeds (3 and 8 mph) whilst standing on the treadmill.

*2.5. The Bassin Anticipation Timer.* The Bassin Anticipation Timer was set up horizontally across the front of the treadmill. This enabled participants to complete the CAT trials whilst walking. The mean time to complete the CAT trials was 60 seconds. Three sections of runway (2.24 m) with the system's LED lights facing the participant were used with the runway sections mounted onto the treadmill. None of the lights on the runway were blanked and the target light was light number 13. The experimental setup is depicted in Figure 1. The sequentially lighted LED lamps illuminate in a linear pattern with movement occurring from right to left. For each trial, scores were recorded in milliseconds (ms) and whether the response was early or late. The start and end speeds remained constant at 3 and 8 miles $h^{-1}$ for all trials. To reduce the likelihood that the participant could internally time the trial, cue delay (visual warning system) was set as random on the timer with a minimum delay of 1 second and a maximum delay of 2 seconds. For each trial, the signal was initiated by the experimenter. The participant was asked to press a trigger button, with their dominant hand, as close to the arrival time of the stimulus at the target location as possible. This is congruent with other research which has examined CAT during exercise [13].

*2.6. Statistical Analysis.* The results are expressed as mean and standard deviation (SD). Each participant's raw scores across each of the stimulus speeds were summarised into three error scores as a means of generating the dependent variables. This is consistent with the recognised protocols using CAT scores [9, 13, 17, 24]. The dependent measures were as follows.

*2.6.1. Absolute Error.* The absolute value of each raw score disregarding whether the response was early or late was calculated. Absolute error provides the best representation of both the individual and combined effects of task characteristics as a whole [17] and as a consequence tends to be the most widely reported CAT outcome variable in the literature [9, 17]. The data for absolute error were however positively skewed (all the values are positive). To correct for skewness, the data set were log transformed as log transforming data in this way has been shown to overcome skewness in previous work [9, 25].

*2.6.2. Variable Error.* The participant's standard deviation from his mean response; this represents the variability/inconsistency of responses. Similar to absolute error, the data for variable error were skewed and therefore data were log transformed as per previous authors [9, 25].

*2.6.3. Constant Error.* The temporal interval (milliseconds) between the arrival of the visual stimulus and the end of the participant's motor response. It represents the mean response of an individual and the direction of error (i.e., early or late) [26].

To compare the effect of rest versus exercise on constant error, absolute error, and variable error, a 2 (rest versus exercise) × 2 (stimulus speeds) × 4 (time intervals, before, at 9 min and 18 min during, and after) repeated measures analysis of variance (ANOVA) was employed. Where significant differences were found, Bonferroni post hoc pairwise comparisons were used to determine where the differences lay. Partial eta squared ($\eta^2$) was also used as a measure of effect size. The Statistical Package for Social Sciences (SPSS, Version 20, Chicago, IL, USA) was used for all analysis and statistical significance was set, a priori, at $P = 0.05$.

## 3. Results

Mean ± SE of absolute, constant, and variable errors (secs) at stimulus speeds of 3 and 8 mph before, at 9 minutes and 18 minutes during, and after 20-minute rest or 20-minute walking at 50% HRR is presented in Table 2.

*3.1. Absolute Error.* Absolute error demonstrated a significant rest versus exercise × stimulus speed × time interaction ($P = 0.0001$, partial $\eta^2 = 0.481$, Figure 2). Absolute error at 9 minutes during exercise was significantly lower than rest at stimulus speeds of 3 mph ($P = 0.006$) and 8 mph ($P = 0.033$). For stimulus speed of 3 mph this trend continued with lower absolute error during exercise at 18 min ($P = 0.0001$) and after exercise ($P = 0.0001$) compared to rest. However, when stimulus speed was 8 mph there was significantly smaller

Table 2: Mean (SE) of absolute, constant, and variable errors (secs) at stimulus speeds of 3 and 8 mph before, at 9 min and 18 min during, and after 20-minute rest or 20-minute walking at 50% HRR.

| | Rest | | | | Exercise | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before | 9 min during | 18 min during | After | Before | 9 min during | 18 min during | After | |
| Absolute error 3 mph (secs) | 0.05 (0.004) | 0.055 (0.003) | 0.054 (0.002) | 0.053 (0.003) | 0.06 (0.004) | 0.043 (0.003) | 0.036 (0.002) | 0.034 (0.001) | $F_{3,45} = 14.385$, $P = 0.0001$, partial $\eta^2 = .481$, rest versus exercise × stimulus speed × time interaction |
| Absolute error 8 mph (secs) | 0.049 (0.003) | 0.054 (0.004) | 0.051 (0.003) | 0.053 (0.003) | 0.051 (0.004) | 0.043 (0.002) | 0.077 (0.006) | 0.041 (0.003) | |
| Constant error 3 mph (secs) | 0.008 (0.006) | 0.012 (0.007) | 0.014 (0.006) | 0.013 (0.006) | 0.004 (0.009) | 0.002 (0.007) | 0.015 (0.004) | 0.013 (0.004) | $F_{3,45} = 9.949$, $P = 0.001$, partial $\eta^2 = .275$, main effect for time (before, during, and after) |
| Constant error 8 mph (secs) | −0.003 (0.007) | 0.007 (0.005) | 0.019 (0.003) | 0.008 (0.007) | 0.002 (0.007) | 0.016 (0.007) | 0.030 (0.01) | 0.015 (0.006) | |
| Variable error 3 mph (secs) | 0.069 (0.005) | 0.063 (0.003) | 0.065 (0.004) | 0.062 (0.006) | 0.07 (0.006) | 0.054 (0.004) | 0.042 (0.002) | 0.041 (0.003) | $F_{3,45} = 12.735$, $P = 0.0001$, partial $\eta^2 = .459$, rest versus exercise × stimulus speed × time interaction |
| Variable error (secs) | 0.057 (0.005) | 0.067 (0.010) | 0.057 (0.004) | 0.063 (0.005) | 0.056 (0.004) | 0.041 (0.003) | 0.087 (0.01) | 0.041 (0.002) | |

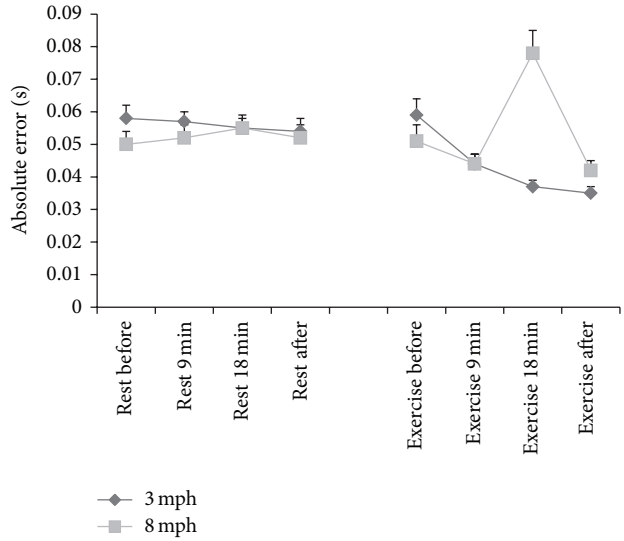


Figure 2: Mean ± SE of absolute error (secs) in rest and exercise conditions, at stimulus speeds of 3 and 8 mph and in rest and exercise conditions.

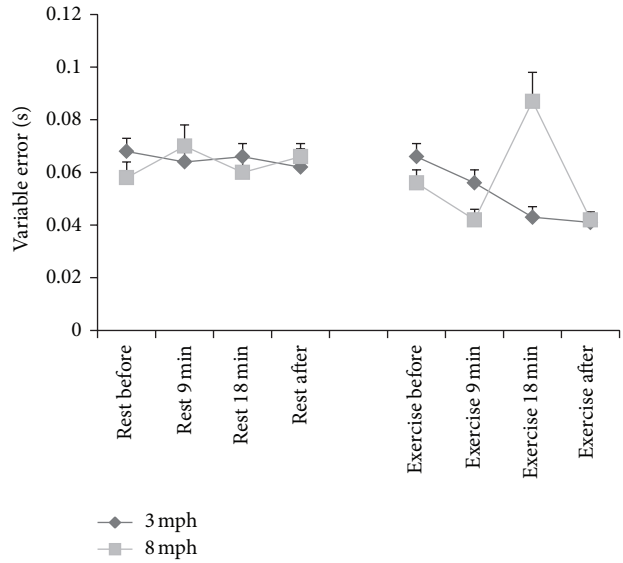


Figure 3: Mean ± SE of variable error (secs) in rest and exercise conditions, at stimulus speeds of 3 and 8 mph and in rest and exercise conditions.

absolute error at 9 min during exercise compared to rest ($P = 0.033$). This trend was reversed at the 18 min time point with absolute error scores during rest being significantly greater than during exercise ($P = 0.003$). After exercise, absolute error scores were significantly lower in the exercise condition compared to the rest condition ($P = 0.014$).

*3.2. Variable Error.* Variable error also revealed a significant rest versus exercise × stimulus speed × time interaction ($P = 0.0001$, partial $\eta^2 = 0.451$, Figure 3). When stimulus speed was 3 mph, variable error was significantly lower during exercise at 18 min ($P = 0.001$) and after exercise ($P = 0.029$) compared to rest. When stimulus speed was 8 mph variable error was significantly lower during exercise compared to rest at 9 min ($P = 0.018$) and after exercise/rest ($P = 0.0001$). However, at 18 min during exercise variable error was significantly higher during exercise compared to rest ($P = 0.026$).

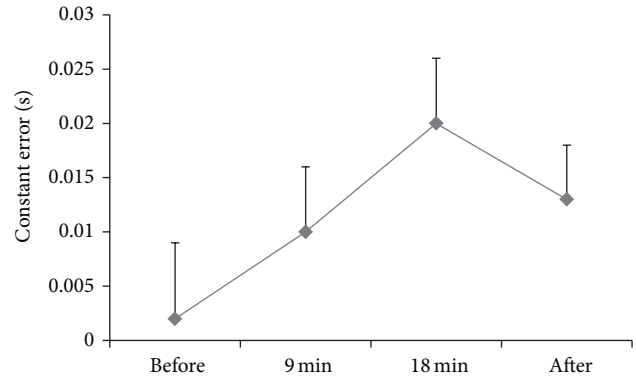


Figure 4: Mean ± SE of the time main effect for constant error (secs).

*3.3. Constant Error.* The repeated measures ANOVA indicated that there were no significant higher-order interactions for constant error. However, there was a significant main effect for time ($P = 0.0001$, partial $\eta^2 = 0.275$, Figure 4). Bonferroni post hoc multiple comparisons indicated that constant error scores were significantly higher at 18 min compared to preexercise/rest ($P = 0.003$) and 9 min ($P = 0.028$).

## 4. Discussion

The purpose of this study was to investigate the effects of different stimulus speeds on CAT performance in older adults before, during, and after exercise in a sample of healthy older adults. The current study suggests that CAT performance was improved during and immediately after exercise (at both 9 minutes and 18 minutes during), compared to rest, but only when stimulus speed was slow (i.e., 3 mph). However, when the stimulus speed of the task was faster (i.e., 8 mph) and consequently more demanding there was a significant increase in absolute and variable errors in the latter half of the 20-minute exercise bout (i.e., poorer performance at 18 minutes during the exercise). The data presented here are novel as no studies to date have examined anticipation timing performance during and after exercise in older adults. Nor has prior work examined any impact of different stimulus speeds on anticipation timing performance in older adults.

The results of the present study add partial support to previous research that has suggested that moderate-intensity exercise results in a significant improvement in performance of cognitive-perceptual, psychomotor, and sport-specific skills [9, 13]. It has also been suggested that moderate-intensity exercise elicits optimal levels of CNS arousal [27, 28] which, among other performance indicators, improves reaction time. Åstrand et al. [29] further add that

moderate-intensity exercise is beneficial to performance due to increased blood flow, warming up of the musculature, and increased speed of nerve transmission within the PNS. In the context of an aging brain, it is possible that this increased blood flow and CNS arousal offset the age related reduction in cerebral blood flow associated with poorer cognitive processing capacity with advancing age [30]. However, in the present study, this suggestion only applies where stimulus speed was slow. When the task was more demanding (via faster stimulus speed) there was an increase in both the error and variability of CAT responses at 18 minutes during the exercise bout (primary task).

In some ways this is not surprising as an increase in dual-task costs occurs when there is a need to manage two streams of similar (e.g., visual) information (i.e., when walking and attending to the CAT task in the present study) compared to when managing two tasks requiring different forms of processing (e.g., one visual and one auditory) [4]. Moreover, errors tend to be higher when task difficulty is greater during dual-task situations that both rely on visual processing in some form [4]. In the present study, the increased physiological demand of walking for 20 minutes, combined with the increased demands of the cognitive task, may have resulted in poorer secondary task performance as changes to gait (i.e., slower walking speed; reduced stride length) would not be possible when walking on a treadmill at a set intensity. This is consistent with assertions previously made by Beurskens and Bock [1].

The loss of central neurons and associated synaptic connections occurs with increasing age in older adults [31]. This, in turn, leads to reduced processing speed and consequently a deficit in the ability to process several tasks simultaneously [31]. This may provide an explanation why older adults' cognitive performance was significantly affected in the present study when the stimulus speed was increased to 8 mph. The fact that CAT tasks were performed during walking may also be fundamental to understanding how exercise might impact on situations in which anticipating correctly is of paramount importance, like crossing a busy road, for example [17]. The present study acted on suggestions by Lambourne and Tomporowski [7] that, in order to understand how exercise impacts on other types of skills, cognitive tests must be conducted during the exercise task rather than after exercise. Lambourne and Tomporowski's [7] suggestions are extremely pertinent to the present study as if only the pre- and postexercise data are considered, the participant responses to both the slow and fast stimulus speeds would appear to show an improvement in timing accuracy after exercise. When data are considered as a continuum or before, during, and after exercise, the effect of the dual-task paradigm becomes apparent.

The magnitude of differences seen at this point, either in comparison to rest data or other data points during, before, or after exercise, is larger than that seen in athletes [9] or young adults [13]. They are also more than double the duration reported for timing of catching actions when stimuli are sighted [32]. Consequently, the differences reported here may be considered as meaningful in the context of anticipation timing in a human movement context. Whether this magnitude of change is partly attributable to aging is yet to be established and future studies comparing the responses of younger to older adults would be useful here. Although no studies to date have examined the effect of exercise on anticipation timing responses in older adults, it is interesting to note that Duncan et al. [13] reported a similar trend in CAT responses to fast stimulus speeds in younger adults but only when exercise intensity was considerably high (90% HRR) than in the present study. Collectively, this supports suggestions by Menant et al. [4], Pothier et al. [5], and Beurskens and Bock [1] that older adults have greater difficulty than younger adults in carrying out walking and cognitive tasks simultaneously due to lack of neural plasticity, where cognitive processing can replace automated sensorimotor processing with higher-order functions.

It is unclear why there might be differing results for constant (directional) and absolute (nondirectional) error scores in the present study. This finding is however not uncommon in the CAT literature [9, 13, 17]. The current results would seem to indicate that increased stimulus speed during exercise results in less accuracy in CAT but in a nonsystematic way. It is also possible that, in line with Kahneman's [33] multidimensional allocation of resources theory, responding to faster stimulus speed as primary task duration increased resulted in increased demands of the concurrent activities with a corresponding greater demand on attentional resources and potentially poorer performance. This aligns with research focused on neural plasticity [3], whereby the demand on cognitive resources allocated to maintaining gait in older adults is kept high (by virtue of a set treadmill walking intensity) leaving less resources available for other activities and resulting in poorer secondary task performance when secondary task demand is higher [14]. For example, the prioritization for postural control over cognitive process, where there is a threat to postural stability [34], results in a situation where cognitive-perceptual tasks cannot be completely attended to until the appropriate postural responses have been initiated (or inhibited) [34]. In the present study, where the secondary task was more demanding, the prioritization of maintaining gait during treadmill walking led to a situation where cognitive workaround strategies that would normally replace sensorimotor processing were not as effective due to high resource allocation demands for both the treadmill walking and secondary (CAT) tasks.

Despite the findings presented here, this study is not without limitation. The task employed in the present study required the participant to briskly walk on a treadmill at a standardised exercise intensity and duration. This intensity equates to a brisk walk at a duration equated with health benefit in older adults [34]. This allowed for locomotive control of the primary task demands, as the participants could not alter the resource allocated to the primary task (i.e., reduction in walking speed as a compensatory measure) when they were required to carry out the cognitive tasks. In the current study the motion of the Bassin Timer moved in a linear fashion from right to left in front of the participant. This may arguably have made the task somewhat different to the typical anticipatory movements made in some aspects of daily life (e.g., catching a ball thrown to an individual;

negotiating a busy shopping precinct) but may be more akin to anticipatory decisions made when crossing a busy road, for example, where a car may typically move linearly past a pedestrian. From an ecological perspective the instances where brisk walking and CAT tasks occur at the same time in general in older adults' lives are not known and therefore the direct application of the present study to the daily lives of older adults remains equivocal. Future research would be beneficial which incorporates nonlinear motion, tasks that better represent the dual-task conditions experienced by older adults, and a requirement to respond to secondary task demands unexpectedly as these task parameters may pose a greater demand on cognitive processes for an aging brain [1].

Finally, the participants in the present study were all apparently healthy, free from disease, and habitually physically active. Whether the responses presented here are similar in older adults who are not physically active or have a reduced cognitive capacity has yet to be established.

The results of the present study suggest that, in a dual-task processing paradigm involving walking and CAT tasks, the stimulus speeds play an important role for older adults, whereby exercise enhances timing performance when stimulus speed is slow but reduces performance when stimulus speed is fast. These findings may be indicative that where gait needs to be maintained, cognitive workaround strategies that would normally replace sensorimotor processing are not as effective when attentional demands of the secondary task are greater.

## Conflict of Interests

The authors register no conflict of interests.

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*Research Article*

# An Influence of Birth Weight, Gestational Age, and Apgar Score on Pattern Visual Evoked Potentials in Children with History of Prematurity

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*Purpose*. The objective of our study was to examine a possible influence of gestational age, birth weight, and Apgar score on amplitudes and latencies of P100 wave in preterm born school-age children. *Materials and Methods*. We examined the following group of school-age children: 28 with history of prematurity (mean age 10.56 ± 1.66 years) and 25 born at term (mean age 11.2 ± 1.94 years). The monocular PVEP was performed in all children. *Results*. The P100 wave amplitudes and latencies significantly differ between preterm born school-age children and those born at term. There was an essential positive linear correlation of the P100 wave amplitudes with birth weight, gestational age, and Apgar score. There were the negative linear correlations of P100 latencies in 15-minute stimulation from O1 and Oz electrode with Apgar score and O1 and O2 electrode with gestational age. *Conclusions*. PVEP responses vary in preterm born children in comparison to term. Low birth weight, early gestational age, and poor baseline output seem to be the predicting factors for the developmental rate of a brain function in children with history of prematurity. Further investigations are necessary to determine perinatal factors that can affect the modified visual system function in preterm born children.

## 1. Introduction

A premature birth of a child entails an insufficient formation of multiple organ structures that might result in their dysfunction [1, 2]. It is known that premature infants exhibit neurodevelopmental delay and reduced growth of the cerebral cortex. Malik et al. showed that glutamatergic neurogenesis continues in the premature infants, and preterm birth suppresses neurogenesis [3]. They suggest hypoxia-mimetic agents might restore neurogenesis, enhance cortical growth, and improve neurodevelopmental outcome of premature infants. Children born preterm are at risk of visual impairment due to cerebral visual impairment, which is caused by damage to the geniculocalcarine pathways and is related to the severity of white matter injury [4]. In preterm infants, the periventricular white matter is particularly susceptible to injury. White matter contains important subcortical pathways including the corticospinal tracts and optic radiations. The visual function deficits seen in children born prematurely may be related to the networks involving the cortical dorsal stream and its connections to the parietal, frontal, and hippocampal areas [5]. On the other hand, despite the immaturity of the visual pathway in preterm infants, Jandó et al. showed that the visual cortex is remarkably ready to accept environmental stimulation right after birth [6]. This early plasticity makes full use of the available extra stimulation time in preterm human infants and results, for example, in an early onset of cortical binocularity [7].

Frequently, children born small for gestational age exhibit poor initial general condition, including onset of a retinopathy of prematurity [1, 2]. Likewise, the microstructure of the

central nervous system diverges in neonates with a gestational age less than 38 weeks from children born at term [8]. Importantly, the formation of the central nervous system does not end in the moment of a birth but persists throughout childhood [9, 10]. Proper development of the central nervous system is determined by morphological growth of the visual cortex until 11 years of age and its metabolic formation until 18 years of age [4, 5]. Extensive researches have been conducted on the visual system function by means of pattern visual evoked potentials (PVEPs), revealing that PVEP responses change in time [11, 12]. Children demonstrate higher latencies and higher amplitudes when compared to adults [13, 14]. However, electrophysiological activity matures [12, 15]. Throughout childhood, decrease in latencies and decrease in amplitudes of P100 wave can be observed [10, 11]. Furthermore, P100 wave presents altered range of values in children with history of prematurity in comparison to those born at term [11]. It has been reported that age-dependent PVEP alterations in preterm born neonates seem to remain in close connection to the structural changes in the visual cortex [15]. Moreover, an anomalous primary conformation of the central nervous system implies its delayed path of development, which might be reflected in modified results of pattern visual evoked potentials [12, 16].

Although changed maturation of the electrophysiological responses caused by prematurity is highly proven, there is lack of objective data if gestational age, birth weight, and Apgar score influence P100 amplitudes and latencies. The present study used pattern visual evoked potentials to examine the function of the visual system in preterm born school-age children. We hypothesized that if the actual outcomes are associated with the history of prematurity, higher latencies and lower amplitudes of P100 wave should be observed in the study group, in comparison to peers born appropriate for gestational age. Furthermore, we wanted to determine whether PVEP parameters correlate with birth weight, gestational age, and Apgar scores.

## 2. Materials and Methods

The current study was performed at the Department of Pediatric Ophthalmology and Strabismus, Medical University of Bialystok, Poland. The study and its testing procedures were approved by the University Ethic Committee and were in accordance with the Declaration of Helsinki.

We examined 28 school-age children with a history of prematurity. The results were compared to controls. Inclusion criteria to the study group were as follows: best corrected visual acuity on 1.0 level and preterm birth. Exclusion criteria were high myopia, optic nerve pathology, any disease affecting the central nervous system, and changes in neonatal transfontanel ultrasonography. For final analysis, 50 eyes were involved, while 2 eyes of 2 patients were excluded because of glaucoma and 1 eye of 2 patients was excluded due to high myopia in one eye. The retina of 18 eyes was treated with laser in infancy.

Twenty-five school-age children born at term were enrolled in the control group (mean age 11.2 ± 1.94 years). Boys make up a 36 and girls a 64 percentage of the test group. No history of diseases affecting optic nerve, retina, or central nervous system was found. Visual acuity was equal to 1.0 in all subjects. PVEPs of those children served as the norms by the electrophysiology lab in the past 5 years.

The PVEP examination was performed in a lab with accordance to ISCEV standards by the use of the Espion Diagnosys equipment. PVEP responses were recorded by 5 gold-plated cup electrodes which were attached according to the 10–20 System of Electrode Placement. Three active electrodes were placed on the occipital scalp (O1: left hemisphere, Oz: midline, and O2: right hemisphere). The ground electrode was located on the vertex. The reference electrode was set on Fz. The patients were seated one meter viewing distance from the monitor (AccuSync 120) on which a black and white checkerboard was displayed. A used black and white checkerboard pattern was 15 and 60 minutes of arc. All checks were square and the number of light and dark squares was equal. A red fixation point was positioned at a corner of four checks which were located at the center of the field. The mean luminance of the checkerboard was 100 cd/m and the contrast between black and white squares was equal to 100%. Reversal rate was equal to 1.999 per sec. Sweeps per result were 80. Low cut-off filter was 2.5 Hz and high cut-off 100 Hz. The average response was obtained from 2 reversals which were adequate in P100 amplitude and latency. The P100 wave was measured from the preceding N75 peak. The monocular stimulation was performed.

*2.1. Statistical Analysis.* Statistic data was processed using STATISTICA Version 10 (StatSoft). The Kolmogorov-Smirnov test (KS-test), chi-square distribution, Student's $t$-test, scatter diagrams, and Pearson's correlation coefficient ($r$) were processed for statistical analysis. KS-test was performed to delimit normality of the distribution. Chi-square distribution was executed to confirm that there are no statistically important differences in percentage of boys and girls between test and control group. Student's $t$-test was accomplished to determine possible age differences between the test and the control group. The P100 wave latencies and amplitudes in 15- and 60-minute pattern stimulation obtained from O1, Oz, and O2 electrode were compared for analogical age in test and control group (Student's $t$-test). Afterwards, correlations were determined between the P100 wave latencies, amplitudes and gestational age, birth weight, and Apgar score. PCC was computed to determine dependencies between variables. Scatter diagrams were prepared to visualize correlations between PVEP parameters gestational age, birth weight, and Apgar score. Differences with a $P$ value less than 0.05 were considered statistically significant.

## 3. Results

Mean age in the study group was 10.56 ± 1.66 years. Boys make up a 52 and girls a 48 percentage of the test group. Mean gestational age was 30 ± 3.54 weeks. Mean birth weight was 1524.4 ± 580.96 grams. Mean Apgar score in 5 minutes was 5.24 ± 2.8.

Table 1: PVEP values in the test group and the control group (Student's $t$-test, $n$: number of eyes).

| PVEP electrode | PVEP parameters | Control group ($n = 50$) Mean ± SD | | Test group ($n = 50$) Mean ± SD | | Significance | |
|---|---|---|---|---|---|---|---|
| | | 15 min | 60 min | 15 min | 60 min | 15 min | 60 min |
| O1 | P100 latency (ms) | 103.36 ± 4.77 | 100.74 ± 5.48 | 110.37 ± 9.74 | 107.64 ± 12.74 | $P < 0.001^*$ | $P < 0.001^*$ |
| Oz | P100 latency (ms) | 103.79 ± 3.84 | 99.35 ± 4.19 | 109.97 ± 9.61 | 105.15 ± 11.02 | $P < 0.001^*$ | $P < 0.001^*$ |
| O2 | P100 latency (ms) | 104.65 ± 4.73 | 100.7 ± 4.81 | 111.52 ± 10.13 | 107.61 ± 11.79 | $P < 0.001^*$ | $P < 0.001^*$ |

*Statistically significant.

Table 2: Correlation of PVEP variables with gestational age (weeks), birth weight (grams), and Apgar score.

| PVEP electrode | PVEP parameters ($n = 50$) | | GA (weeks) | | Birth weight (grams) | | Apgar score | |
|---|---|---|---|---|---|---|---|---|
| | | | 15 min | 60 min | 15 min | 60 min | 15 min | 60 min |
| O1 | P100 latency (ms) | $r$ | $-0.34^*$ | $-0.04$ | $-0.23$ | $-0.02$ | $-0.4^*$ | $-0.14$ |
| | P100 amplitude ($\mu$m) | $r$ | $0.27^*$ | $0.29^*$ | $0.3^*$ | $0.31^*$ | $0.3^*$ | $0.58^*$ |
| Oz | P100 latency (ms) | $r$ | $-0.21$ | $-0.13$ | $-0.10$ | $-0.1$ | $-0.3^*$ | $-0.18$ |
| | P100 amplitude ($\mu$m) | $r$ | $0.53^*$ | $0.50^*$ | $0.59^*$ | $0.55^*$ | $0.37^*$ | $0.58^*$ |
| O2 | P100 latency (ms) | $r$ | $-0.27^*$ | $-0.15$ | $-0.19$ | $-0.15$ | $-0.26$ | $-0.16$ |
| | P100 amplitude ($\mu$m) | $r$ | $0.37^*$ | $0.33^*$ | $0.47^*$ | $0.40^*$ | $0.34^*$ | $0.4^*$ |

GA: gestational age; $n$: number of eyes; $r$: Pearson's correlation coefficient; *correlation.

KS-test confirmed that data was distributed normally. Chi-square distribution showed no statistically important differences in percentage of boys and girls between test and control group. Student's $t$-test revealed no statistically important age differences between the test and the control group.

*3.1. P100 Latencies.* The latencies of P100 wave in 15- and 60-minute check stimulation vary in school children with history of prematurity in comparison to their peers (Student's $t$-test). The P100 latency was delayed in the study group in comparison to controls (Table 1).

Pearson's correlation coefficient was determined to evaluate the relationship of the P100 wave latencies obtained from O1, Oz, and O2 electrode with gestational age, birth weight, and Apgar score. There was a negative correlation between the P100 latency in 15-minute check stimuli and gestational age, birth weight, and Apgar score. Also P100 latencies in 60-minute check stimuli correlated negatively with gestational age, birth weight, and Apgar score. To conclude, there was a negative relationship between P100 latencies and gestational age, birth weight, and Apgar score. Higher results of P100 wave latencies were correlated with earlier gestational age, smaller birth weight, and lower Apgar score. However, there were only correlations in 15-minute check stimuli with amount of Apgar score (obtained from O1 and Oz electrode) and gestational age (obtained from O1 and O2 electrode) (Table 2). Scatter diagrams highlight the essential correlations (Figures 1 and 2).

*3.2. P100 Amplitudes.* The P100 wave amplitudes differ between preterm born school-age children and those born appropriate for gestational age (Student's $t$-test). The P100 amplitudes were smaller in the study group in comparison

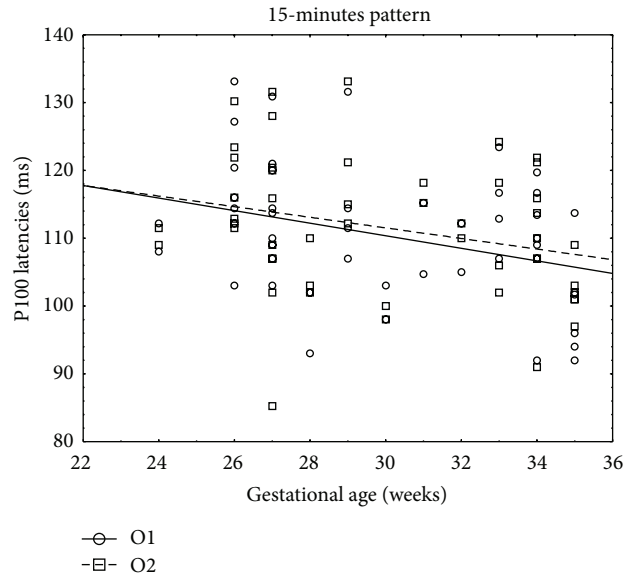


Figure 1: Scatter diagram showing a negative linear correlation between P100 latencies (ms) and birth weight (grams) in 15-minute pattern stimuli.

to the control group: from O1 electrode (in $\mu$m): 7.08 ± 2.87 versus 14.75 ± 5.38 in 15 min. ($P < 0.001$) and 8.31 ± 3.27 versus 14.88 ± 4.77 in 60 min. ($P < 0.001$); from Oz electrode: 11.67 ± 5.98 versus 24.96 ± 9.62 in 15 min. ($P < 0.001$) and 12.71 ± 5.46 versus 25.3 ± 8.44 in 60 min. ($P < 0.001$); from O2 electrode: 7.99 ± 5.14 versus 15.24 ± 6.33 in 15 min. ($P < 0.001$) and 8.86 ± 5.63 versus 15.67 ± 6.04 in 60 min. ($P < 0.001$) (Figure 3).

To assess the correspondence of the P100 wave amplitude values in 15- and 60-minute pattern stimulation (obtained

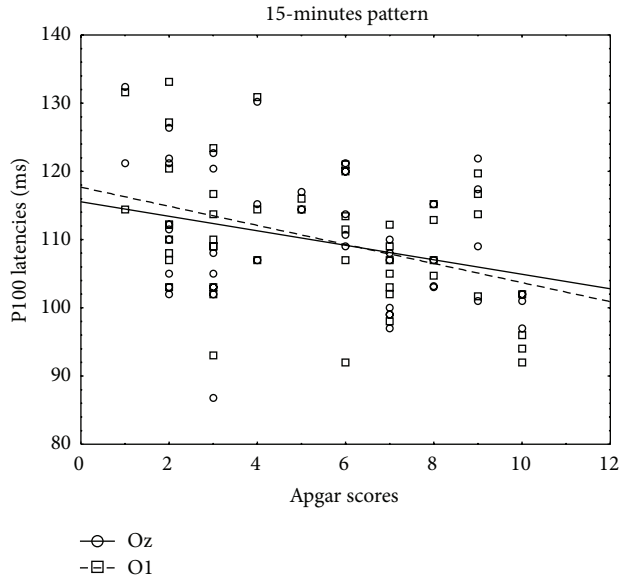


Figure 2: Scatter diagram showing a negative linear correlation between P100 latencies (ms) and amount of Apgar score in 15-minute pattern stimuli.

from O1, Oz, and O2 electrode) with gestational age, birth weight, and Apgar score, a PCC was gauged. There was a positive correlation between P100 amplitudes in 15-minute check stimulation and gestational age, birth weight, and amount of Apgar score. Also the values of P100 amplitudes in 60-minute pattern stimulation correlated positively with gestational age, birth weight, and amount of Apgar score. Overall, there was a positive correlation of the P100 amplitudes with gestational age, birth weight, and Apgar score. Higher P100 wave amplitudes values were correlated with later gestational age, greater birth weight, and higher amount of Apgar score (Table 2). Scatter diagrams highlight the correlations (Figures 4, 5, and 6).

## 4. Discussion

Brain development in the late preterm period is essential for proper cognitive abilities [8, 17]. It is only 38–40 weeks after conception that elongation of dendrites and proper dendritic branching is completed [18, 19]. The influence of the preterm birth and low gestational weight on the global and regional brain volume abnormalities was proven by many authors [8, 16, 20]. Moreover, Peterson et al. have demonstrated that these brain volume differences between term and preterm born children persisted until later childhood [20]. Peterson et al. and Ball et al. described the association of lower mean diffusivity in occipital lobes with preterm birth [8, 20]. MRI investigations performed by Parikh et al. revealed decreased regional and total brain tissue volume in extremely low birth infants [16]. It is known that oxygen contributes to the pathogenesis of neonatal brain damage, leading to neurocognitive impairment of prematurely born infants in later life. Felderhoff-Mueser reported that short exposures to nonphysiologic oxygen levels cause oxidative stress and can trigger apoptotic neurodegeneration in the developing brains of infant rodents [21]. Sifringer et al. reported that hyperoxia triggers a marked increase in the active caspase-2 expression, resulting in an initiation of the intrinsic apoptotic pathway with upregulation of key proteins [22].

Maturation of the visual system is still thoroughly studied by neurologists and ophthalmologists. Many researchers have investigated global and microstructural brain tissue changes in the development of the central nervous system and age-dependent alterations of visual evoked potentials responses [8–12, 15, 16, 18–20]. Also the evolutional differences between prematurely born children and those born appropriate for gestational age are still substantial [11, 16, 23–25]. However, the main current and future task for neurological and ophthalmological research is the exploration of the factors that can affect the modified visual system function in preterm born subjects [23].

The structural changes in the central nervous system seem to be reflected in the PVEPs alterations [15]. In our study we observed that there was an essential positive linear correlation of the P100 wave amplitudes with birth weight, gestational age, and Apgar score. We also noticed the negative linear correlation of P100 latencies in 15 minutes simulation with Apgar score and gestational age. Sokol and Jones explored that children born preterm had shorter latencies of P100 wave than children born appropriate for gestational age [11]. Inversely, Ruberto et al. revealed that premature newborns had delayed latencies of P100 wave in comparison to neonates born at term [24]. Although Peterson et al.'s research on central nervous system development confirmed that structural brain changes persisted until later childhood, Nilsson et al. ascertained that children born small for gestational age show no signs of accelerated neurophysiological maturation in preschool period [20, 25]. Moreover, Atkinson et al. demonstrated that visual development of children with only the history of prematurity is unchanged even in the neonatal period. However, the authors highlighted that there is a possible influence of perinatal damage factors which were reflected in modified PVEP responses [23].

The outcomes, which we achieved in our study, appear to be consistent with previous reports [9, 10, 15, 16, 20]. The P100 wave latencies were delayed and amplitudes were statistically smaller in the test group in comparison to controls. Increasing amplitudes and decreasing latencies of P100 wave in school-age children with history of prematurity are similar to Brecelj et al.'s results, obtained in the study on maturation of the electrophysiological responses [12, 15]. Similarly, our outcomes also seem to correspond with results obtained in research on structural development of the central nervous system described by Garey and de Courten and metabolic formation of the brain described by Huttenlocher et al. [9, 10]. Lower P100 amplitudes in the test group and the correlation between P100 amplitudes and birth weight, gestational age, and Apgar score might reflect a decrease in the total brain tissue volume in preterm born children described by Parikh et al. [16]. Moreover, Peterson et al.'s studies on the persistence of brain changes in children with a history of prematurity until childhood seem to confirm that correspondence [20].

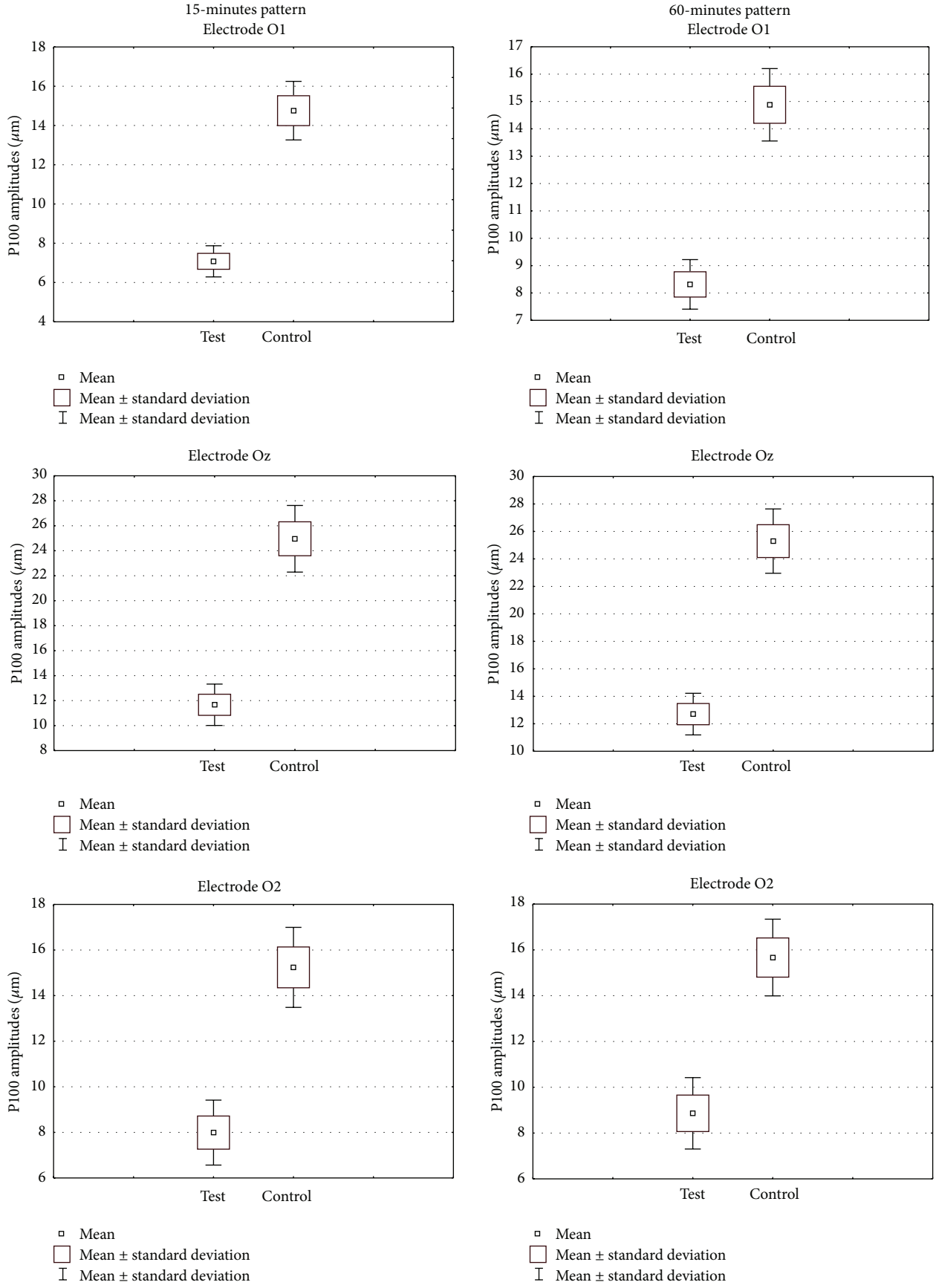


Figure 3: Continued.

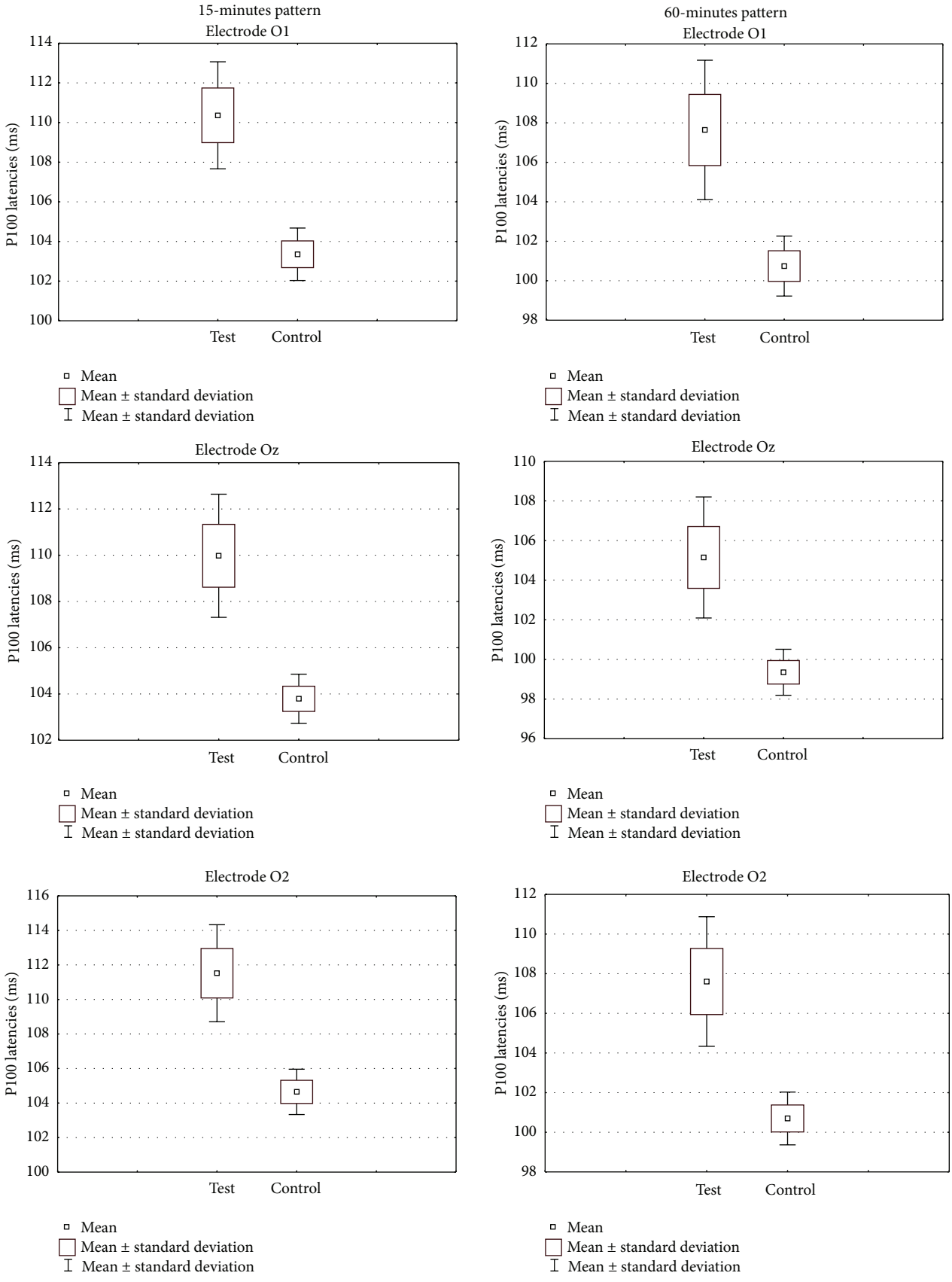


Figure 3: Whiskers diagrams highlight P100 wave amplitudes ($\mu$m) and P100 wave latencies (ms) significant differences between the test and the control group.

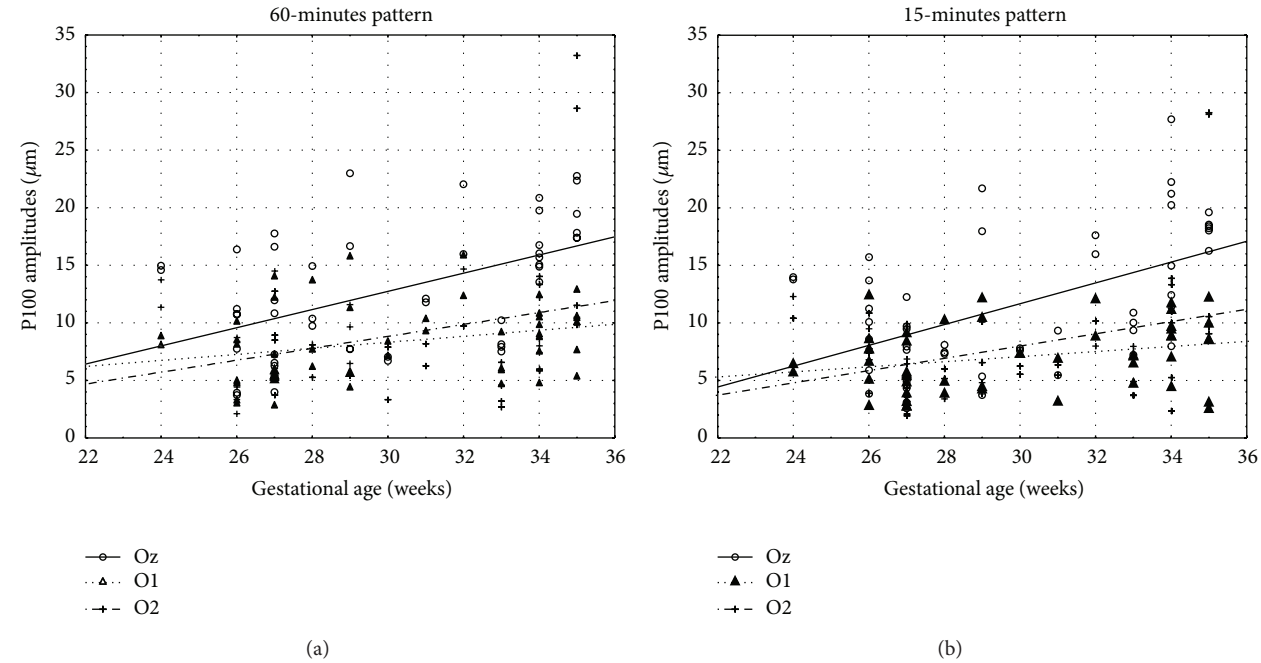


Figure 4: Scatter diagram showing a positive linear correlation between P100 amplitudes ($\mu$m) and gestational age (weeks) in 15- and 60-minute pattern stimuli.

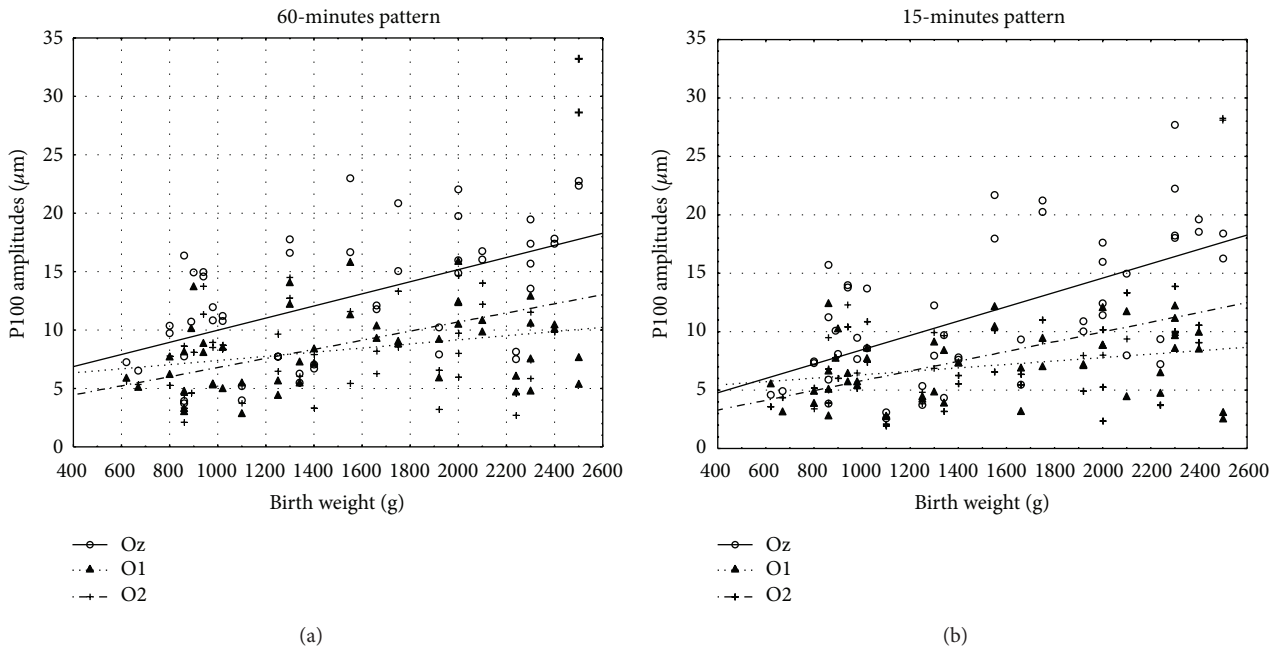


Figure 5: Scatter diagram showing a positive linear correlation between P100 amplitudes ($\mu$m) and birth weight (grams) in 15- and 60-minute pattern stimuli.

The correlations between P100 latencies (15-minute check stimuli) and Apgar score or low birth weight demonstrate that initial general condition of a preterm born child has a significant influence on electrophysiological responses. That might confirm Atkinson's theory that there are perinatal damage factors that change PVEP responses [23].

Also the researches on flash visual evoked potentials (FVEPs) seem to correspond with our study on PVEP values. Giapros et al. concluded that FVEP developmental pattern of preterm infants was similar to that of healthy full-term infants; the former had deficits in visual electrophysiologic maturation, especially for very low birth weight children [26].

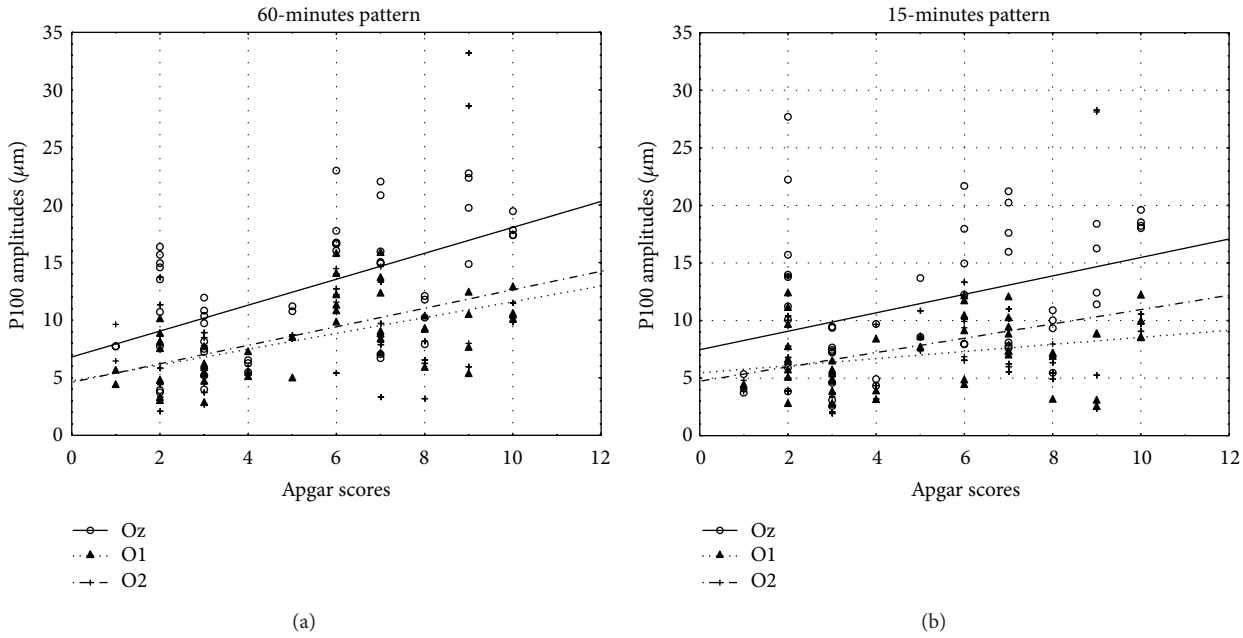


Figure 6: Scatter diagram showing a positive linear correlation between P100 amplitudes ($\mu$m) and amount of Apgar score in 15- and 60-minute pattern stimuli.

Feng et al. noticed that latency of the P2 main wave on FVEPs was delayed more significantly in premature infants than in full-term infants [27]. They ascertained that the visual functional development was delayed in preterm born infants, especially in infants with very low birth weight and in gestational age less than 32 weeks [27, 28]. However, FVEP is less precise examination than PVEP; thereby PVEP should be the first ordered testing [29].

In our study we examined preterm born school-age children, with mean age of 10.56 ± 1.66 years. There are only few publications concerning the analysis of the PVEP in a similar age group. Feng et al. evaluated PVEP in 61 preterm preschoolers with average intelligence quotients and compared them to 41 normal children [30]. The PVEP P100 wave latencies were significantly prolonged in the very low birth weight group compared with the controls, while showing delay in the low birth weight group. They concluded that preterm preschoolers with an average cognition capability are at the risk of defect in visual-spatial perception. In their opinion PVEP may provide an objective and convenient measurement in detecting the problem of visual perception in children. O'Reilly et al. examined 12 preterm born children and 12 born full-term controls at 8–12 years of age [31]. On the contrary, they observed that the P100 component of the PVEP showed a significantly shorter latency in the preterm compared with the full-term participants. Ruberto et al. tried to identify subclinical morphologic or functional defects in premature infants born between 28 and 35 weeks [7]. They evaluated PVEP, OCT, and HRT in 14 premature newborns at birth and subsequently when they were young children (mean age 7.5 ± 0.2 years). Multiple significant $P$ values were found in the VEP P100 peak time and steady-state amplitudes at the time of birth, but not at the time of the morphologic analysis. They also observed statistically significant changes of the optic nerve in OCT and HRT. They concluded that healthy, premature newborns may have morphologic abnormalities of the optic nerve and these abnormalities do not cause visual acuity or functional decreases.

Our study confirmed that PVEP responses differed between preterm born school-age children and children born at term. However, we did not examine if there are changes in P100 parameters during school-age period, because we believe that the maturation of pattern visual evoked potentials is highly proven. The aim of our study was to objectivize the current knowledge about the influence of prematurity on pattern visual evoked potentials parameters. We believe that strong correlations between low birth weight, early gestational age, Apgar score, and P100 amplitudes or some P100 latencies seem to be the evidence that premature birth impacts effects on visual evoked responses. Furthermore, our research proves that this influence persists even until school-age. Positive linear correlations between P100 amplitudes and gestational age, Apgar score, and birth weight prove without a doubt their role as predicting factors for the developmental rate of a brain function in children with a history of prematurity. The negative linear correlations of P100 latencies in 15 minutes stimulation from O1 and Oz electrode with Apgar score, and from O1 and O2 electrode with gestational age, might reflect the delayed electrophysiological maturation for small pattern in comparison to the big one [32]. Nevertheless, further similar researches in a group of younger children that we examined had to be performed to validate this hypothesis.

Still, we acknowledge that our study has some limitations. Firstly, the number of patients in the control group and the study group was rather small. Secondly, the small amount of results prevents us from subdividing measurements.

Therefore our study mixes low, very low, and extremely low birth weights. Also boys and girls groups are not assigned. The difference in the number of patients in the mentioned subgroups renders receiving credible and statistically important results impossible; the normality of data distribution cannot be achieved.

The data of PVEP responses in school-age children with history of prematurity is still lacking. Commonly, preterm born children with good visual acuity are not remaining under the supervision of an ophthalmologist. Further investigations are necessary to determine the perinatal factors that can affect the modified visual system function in preterm born persons. The current neonatal knowledge enables physicians to save lives of children with increasingly lower gestational age and birth weight. A matter of special interest will be the influence of low, very low, and extremely low birth weight and very small gestational age on PVEP responses. However, also different perinatal factors, especially changes in perinatal care over the past 30 years, will be the issue of increasing importance.

## 5. Conclusions

PVEP responses vary in preterm born children in comparison to their peers born appropriate for gestational age. Low birth weight, early gestational age, and poor baseline output seem to be the predicting factors for the developmental rate of a brain function in children with history of prematurity. Further investigations are necessary to determine perinatal factors that can affect the modified visual system function in preterm born persons.

## Conflict of Interests

There is no conflict of interests to disclose.

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*Research Article*

# Age-Related Reduced Somatosensory Gating Is Associated with Altered Alpha Frequency Desynchronization

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Sensory gating (SG), referring to an attenuated neural response to the second identical stimulus, is considered as preattentive processing in the central nervous system to filter redundant sensory inputs. Insufficient somatosensory SG has been found in the aged adults, particularly in the secondary somatosensory cortex (SII). However, it remains unclear which variables leading to the age-related somatosensory SG decline. There has been evidence showing a relationship between brain oscillations and cortical evoked excitability. Thus, this study used whole-head magnetoencephalography to record responses to paired-pulse electrical stimulation to the left median nerve in healthy young and elderly participants to test whether insufficient stimulus 1- (S1-) induced event-related desynchronization (ERD) contributes to a less-suppressed stimulus 2- (S2-) evoked response. Our analysis revealed that the minimum norm estimates showed age-related reduction of SG in the bilateral SII regions. Spectral power analysis showed that the elderly demonstrated significantly reduced alpha ERD in the contralateral SII (SIIc). Moreover, it was striking to note that lower S1-induced alpha ERD was associated with higher S2-evoked amplitudes in the SIIc among the aged adults. Conclusively, our findings suggest that age-related decline of somatosensory SG is partially attributed to the altered S1-induced oscillatory activity.

## 1. Introduction

Despite the continuous attention to the age-related changes in the higher hierarchical cognitive function, recent imaging studies have shown that the early-phase perceptual process, for example, cortical inhibition or sensory gating (SG), is also modulated by aging [1–7]. Most importantly, this cortical disinhibition has been linked to the aberrant neuropsychological or behavioral performance [5, 8, 9].

Compelling evidence shows that electrical stimulation to the median nerve elicits synchronous cortical reactivity in the primary somatosensory cortex (SI) and bilateral secondary somatosensory cortex (SII) [10–14]. By using paired-pulse electrical stimulation, in which two stimulus pulses in close succession are presented, it has been extensively applied to study the functional integrity of cortical inhibition or excitability in various clinical disorders, such as schizophrenia [15], traumatic brain injury [16], complex regional pain syndrome [17], dystonia [18], migraine [19], and aging [3, 5]. Quantitatively, SG is measured as the amplitude ratio of stimulus 2-evoked responses over stimulus 1-evoked responses (S2/S1) [20]. A larger S2/S1 ratio is indicative of

reduced cortical inhibition. With this technique, one previous event-related potential (ERP) study has revealed an age-associated SG defect in the human SI [5]. Very recently, our magnetoencephalographic (MEG) study by applying equivalent current dipole (ECD) modeling has demonstrated that the neurophysiological responses of the SII are particularly vulnerable to aging in terms of cortical SG [2].

In addition to phase-locked evoked responses, non-phase-locked brain oscillations might be implicated in the basic somatosensory perceptual processing [21]. Cortical oscillation is considered to reflect the excitability of thalamocortical systems and can be modulated by exogenous or endogenous events [22]. Event-related desynchronization (ERD) represents a decrease in synchronization of a specific frequency in relation to the activation of the somatosensory system [23–25]. Previous studies have reported significant alpha and/or beta ERD in the SI [26–29] and SII [30–32] following electrical or laser stimulation among the young healthy adults. However, it still remains unclear whether the somatosensory ERD is affected by physiological aging.

Although previous literature has demonstrated reduced somatosensory SG as a function of age, the possible contributing factors or variables are obscure. An association between oscillatory activity and cortical excitability in the sensorimotor cortex has been shown [31, 33, 34]. Here, we were intrigued to examine whether S1-induced ERD activity serves as a possible factor to account for the age-related alterations in the S2-evoked excitability.

Specifically, this MEG study aimed (1) to investigate the effects of aging on somatosensory cortical alpha and beta ERD induced by median nerve stimulation and (2) to determine the relation between S1-induced ERD and S2-evoked responses. Our working hypothesis was that the elderly might demonstrate reduced somatosensory SG and ERD magnitude. Finally, we predicted that a less-suppressed S2-evoked activity in the aged adults might be associated with deficient S1-induced ERD.

## 2. Methods

*2.1. Participants.* Eighteen young (mean 23.7 ± 0.9 years) and fifteen elderly (mean 68.5 ± 2.2 years) healthy male volunteers participated in this study. All subjects were right-handed with no history of neurological or psychiatric disorders. The majority of these participants were from our previous research project [2]. The Institutional Review Board of the Taipei Veterans General Hospital approved the protocol, and informed consent was obtained from all subjects.

*2.2. Paradigm.* The left median nerve was stimulated at the wrist with 0.2 ms constant-current square-wave pulses by an electrical stimulator (Konstantstrom Stimulator, Schwind, Erlangen, Germany). Stimulus intensity was set at 20% above the motor threshold for eliciting a visible twitch of the abductor pollicis brevis muscle (young = 4.4 ± 0.1 mA, elderly = 4.6 ± 0.1 mA; $P = 0.29$; unpaired two-tailed $t$-test). Stimuli were delivered in pairs with an interstimulus interval (ISI) of 0.5 s and an interpair interval of 8 s. The ISI of ~0.5 s allowed us to simultaneously examine the whole somatosensory system, including SI and bilateral SII areas [2, 15, 31]. Subjects were asked to ignore the stimulation and focus on a silent video, in which way we could examine the preattentive responses without contamination by anticipation effects.

*2.3. MEG Recordings.* The cortical magnetic fields were recorded with whole-head 306-channel MEG (Vectorview, Elekta Neuromag, Helsinki, Finland). The data from planar gradiometers of this device, which detect the largest signal directly above the activated cerebral areas [35], were analyzed. The coil locations in relation to the anatomical landmarks (left preauricular point, right preauricular point, and nasion) were determined with a 3D digitizer.

The MEG signals were digitized at a sampling rate of 500 Hz, with an online bandpass of [0.1, 200] Hz. An interval of 0.5 s, including a prestimulus baseline of 0.1 s, was evaluated. Epochs contaminated by prominent electrooculogram signals (>300 $\mu$V) and MEG artifacts (>3000 fT/cm) were automatically excluded from averaging. At least 100 artifact-free evoked S1 and S2 responses were averaged online.

*2.4. Source Estimation.* The averaged data were offline filtered with a bandpass of [0.1, 120] Hz and a 100 ms baseline correction. We applied a distributed minimum norm estimate (MNE) source modeling to reconstruct evoked responses and identified three regions of interest (ROIs): SI and contralateral (SIIc) and ipsilateral (SIIi) secondary somatosensory cortex.

The modeling of the cortical spatiotemporal dynamics of somatosensory evoked responses was obtained with Brainstorm [36]. The segmentation of head tissues from individual T1-weighted magnetic resonance imaging (MRI, GE Discovery MR 750 3T with TR 9.4 ms, TE 4 ms, recording matrix 256_256 pixels, field of view 256 mm, slice thickness 1 mm) volume data was obtained with BrainVisa (http://brainvisa.info/). The representation of folded cortical surface was used to resolve the forward problem by applying an overlapping-sphere model, which derives the strength of a set of electric dipoles located at the cortical surface [37]. For each participant, cortically constrained source imaging was performed using the depth-weighted MNE [38, 39] model of Brainstorm, with default parameter settings, over a set of ~7500 elementary current dipoles distributed over the individual cortical envelope. The individual source maps were geometrically registered to the Montreal Neurological Institute (MNI) brain template (Colin27) using Brainstorm's multilinear registration technique, with default parameters.

The MNE source maps were obtained for each participant and each stimulus condition and group-averaged onto the aligned cortical surface of the Colin27 brain template. Based on the grand-averaged waveform time series and cortical activation, a cluster of 30 vertices corresponding to 4-5 $cm^2$ was manually selected to define each ROI.

The time-resolved magnitude of each elementary source was normalized to its fluctuations over baseline, yielding a set of $Z$-scored time series at each cortical location [40, 41]. The $Z$-score values were rectified to detect absolute magnitude

changes above baseline levels, and peak responses to S1 and S2 of each ROI were extracted for subsequent analysis. The degree of SG was quantified as the ratio of the strength of S2 divided by S1.

*2.5. Spectral Analysis.* Each raw single trial in the selected ROIs was analyzed by using Morlet wavelet-based time-frequency approach in Brainstorm software. Epochs of 2.5 s duration with 1.0 s preceding S1 and 1.0 s following S2 were created. Due to the longer peak latency of ERS (~≧0.7 s) [23, 25] and our design of 0.5 s ISI, this study specifically focused on the S1-induced ERD responses.

In the ERD computation, the alpha (8 to 13 Hz) and beta (14 to 30 Hz) bands which exhibited the most reduced activity (0.0 s to 0.5 s following S1) were identified. The averaged baseline power density (−0.9 s to −0.5 s before S1) was calculated after the $Z$-score correction. We selected peak amplitudes of the most reactive frequency bands (2 Hz) [25] of alpha and beta rhythms and compared them with respect to the baseline power level in each individual.

*2.6. Statistical Analysis.* All the data were presented as mean ± standard error of the mean (SEM). Prior to the statistical analysis, all variables were normal distributed as indicated by the Kolmogorov-Smirnov test ($P > 0.05$). The effects of age on SG and ERD were calculated by independent $t$-test. The relationship between S1-induced ERD and S2-evoked responses was evaluated by Pearson's correlation coefficients. All the analyses were performed with the SPSS statistical package (version 13.0). $P$ values of <0.05 were set as the significant threshold.

## 3. Results

*3.1. Somatosensory SG.* Figure 1(a) shows the butterfly plot of somatosensory evoked responses to S1 in one young participant. The prominent P35m of SI was followed by the longer latency responses in the SII regions. The upper panel of Figure 1(b) exhibits the MNE source reconstruction of the selected latencies of 34 ms, 90 ms, and 122 ms. The SI responses were generated in the postcentral wall of central fissure and the SII responses were generated in the upper bank of the Sylvian fissure in the parietal operculum. The lower panel of Figure 1(b) demonstrates the source strength as a function of time in these three ROIs of the same subject. The S2-evoked responses (blue trace) were smaller than S1-evoked responses (red trace).

SG ratios were calculated from each individual and compared between groups. The statistical results show significant higher SG ratios of SIIc ($P = 0.033$) and SIIi ($P = 0.023$) in the elderly group compared to the younger group (Figure 2).

*3.2. Somatosensory ERD.* Due to the obvious between-group differences in the bilateral SII regions, we then concentrated on the effects of aging on S1-induced ERD reactivity in these neural substrates. Figure 3 displays the grand-averaged time-frequency representations of alpha (Figure 3(a)) and beta (Figure 3(b)) rhythms over the time interval of 1.0 s before S1 and 1.0 s after S2 in SIIc and SIIi. The plots below each spectral representation exhibit the grand-averaged temporal dynamics of the most reactive frequency ranges (2 Hz) in terms of alpha and beta oscillations. The white squares show the most prominent S1-induced ERD reactivity.

Table 1: Mean (SEM) ERD reactive frequency for alpha and beta rhythms.

| Region | Alpha | | Beta | |
|---|---|---|---|---|
| | Young | Elderly | Young | Elderly |
| SIIc | 11.3 0.24 | 11.4 0.24 | 19.0 0.82 | 19.1 0.87 |
| SIIi | 10.9 0.83 | 11.0 0.35 | 17.7 0.69 | 17.9 0.63 |

Table 1 lists the averaged ERD-reactive frequency for alpha and beta rhythms. There were no significant differences between young and elderly participants regarding the ERD-reactive frequencies.

Figure 4 shows the mean peak values of alpha and beta ERD with respect to the baseline power. Compared to the younger subjects, the elderly exhibited significantly reduced amplitude of alpha ERD in SIIc ($P = 0.014$). We did not find significant between-group differences in terms of alpha ERD in SIIi and beta ERD in bilateral SII regions.

*3.3. Correlation between S1-Induced ERD and S2-Evoked Responses.* Given the pronounced reduction of alpha ERD in the elderly adults, we then tested whether S1-induced oscillatory responses influence the performance of S2-evoked reactivity. Lower S1-induced alpha ERD was associated with higher S2-evoked amplitude in SIIc ($r = 0.46$, $P = 0.044$) among the elderly participants, as shown in Figure 5.

## 4. Discussion

To obtain insight into the age-related alterations of cortical inhibition in the human somatosensory system, we applied paired-pulse electrical stimulation to the left median nerve, and our results revealed several important findings. Firstly, by using MNE source modeling, the elderly demonstrated reduced SG in bilateral SII regions, replicating our previous ECD results. Secondly, based on the time-frequency approach, we found age-related reduction of alpha ERD amplitude in the SIIc. Lastly, higher S2-evoked responses were associated with reduced S1-induced alpha ERD amplitudes among the elderly participants, especially in the SIIc area. A higher S2-evoked response could be regarded as poor suppression to repetitive stimuli.

The present MNE data demonstrated higher SG ratios of bilateral SII areas in the elderly adults compared to the younger participants, which is consistent with our previous results [2]. These findings highlight somatosensory SG as a prominent manifestation during the late-age stage, particularly in the higher-order SII neural substrates. By calculating the number of dendritic spines and synaptic density, it has been reported that the association areas are more vulnerable to aging processing compared to the primary sensory cortices [42]. Moreover, one functional magnetic resonance imaging

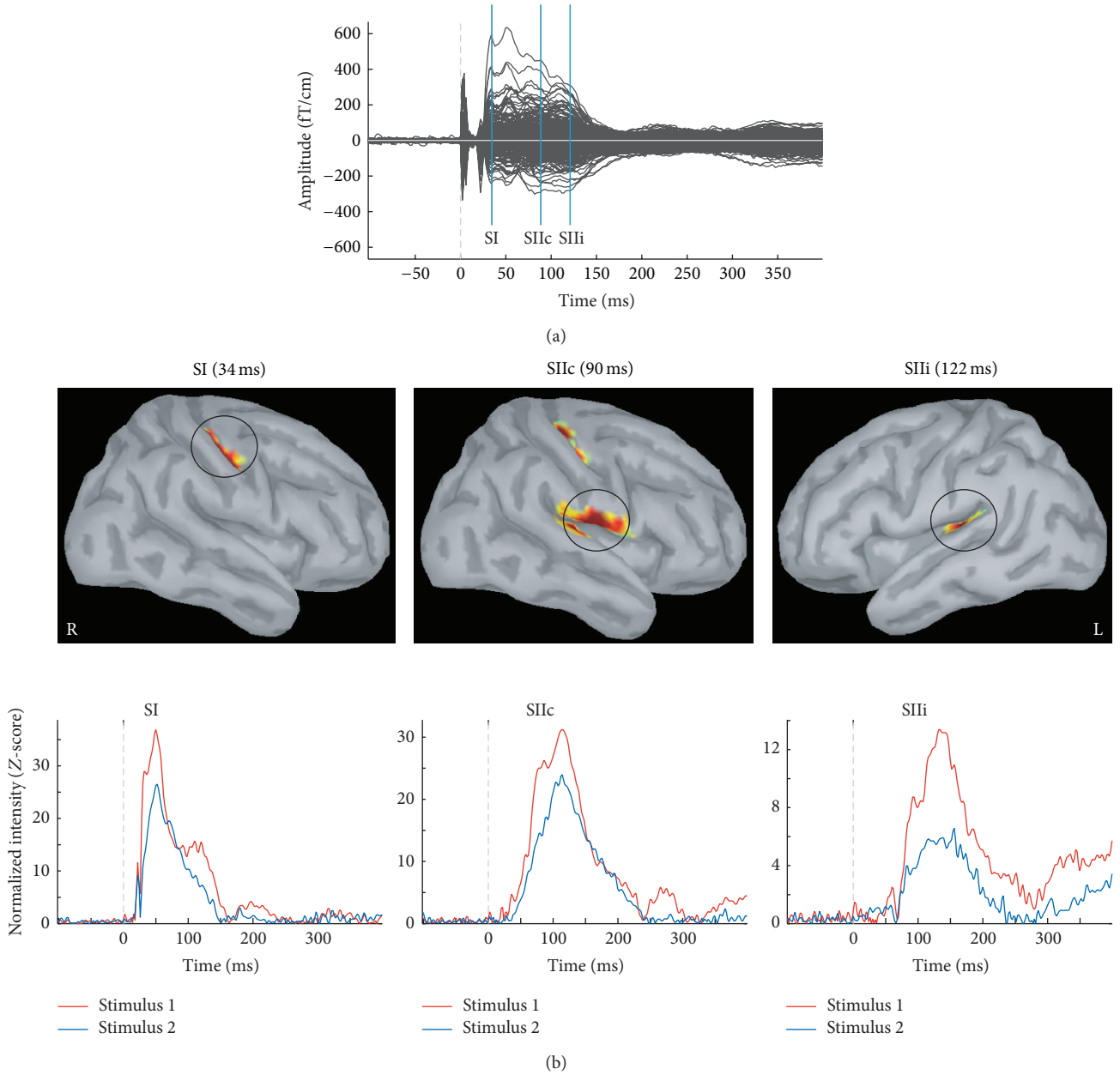
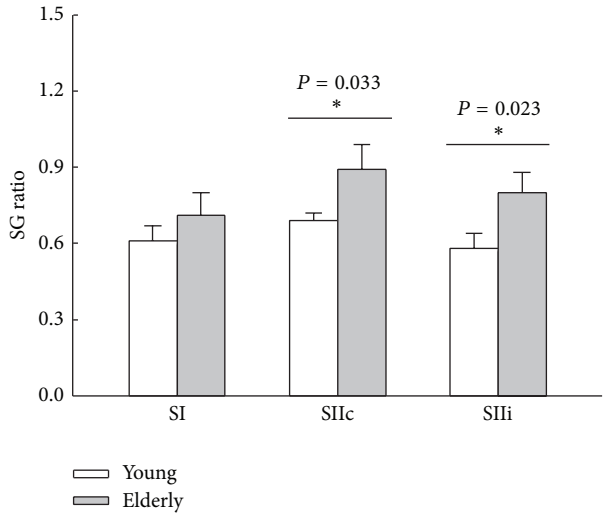



Figure 1: (a) Somatosensory evoked fields to electrical stimulus 1 in one young representative subject. The early primary somatosensory response (SI) is followed by longer latency contralateral (SIIc) and ipsilateral (SIIi) secondary somatosensory responses. (b) Upper panel: three regions of interest (ROIs, 4 to 5 $cm^2$) on the Montreal Neurological Institute Colin27 brain template; lower panel: the temporal dynamics of the minimum norm estimate (MNE) in response to stimulus 1 and stimulus 2 are extracted from the selected ROIs.

study with dynamic causal modeling has delineated that somatosensory information conveyed in hierarchy but in parallel from thalamus to both SI and SII [43]. This observation supported our notion that SII might be independently affected by aging processes.

By using short stimulus onset asynchrony (i.e., 30 ms), one previous ERP report has shown age-associated decline of SG in the SI. The reduction of cortical inhibition also correlated with impairment of two-point discrimination performance in the aged participants [5]. Although the early somatosensory evoked response, N20m, has been proven to recover to the saturated amplitude with an ISI of less than 100 ms [44, 45], our selection of ISI of 500 ms allowed us to examine P35m of SI and SII simultaneously [15]. Most importantly, a recent MEG study has revealed a superior signal-to-noise ratio for P35m at an ISI of 500 ms than other tested conditions, which lent support to the rationale of our design [29]. Collectively, our results of age-related somatosensory cortical disinhibition were in favor of *inhibition deficit* hypothesis in aging brains [6, 7, 46–49].

To the best of our knowledge, this is the first MEG study to investigate the effects of aging on spectral power




| | SI | SIIc | SIIi |
|---|---|---|---|
| Young | 0.61 (0.06) | 0.69 (0.03) | 0.58 (0.06) |
| Elderly | 0.71 (0.09) | 0.89 (0.10) | 0.80 (0.08) |

FIGURE 2: The statistical comparisons between young and elderly individuals in terms of sensory gating (SG) ratio in SI, SIIc, and SIIi areas. The bar above each column indicates the standard error of the mean (SEM).

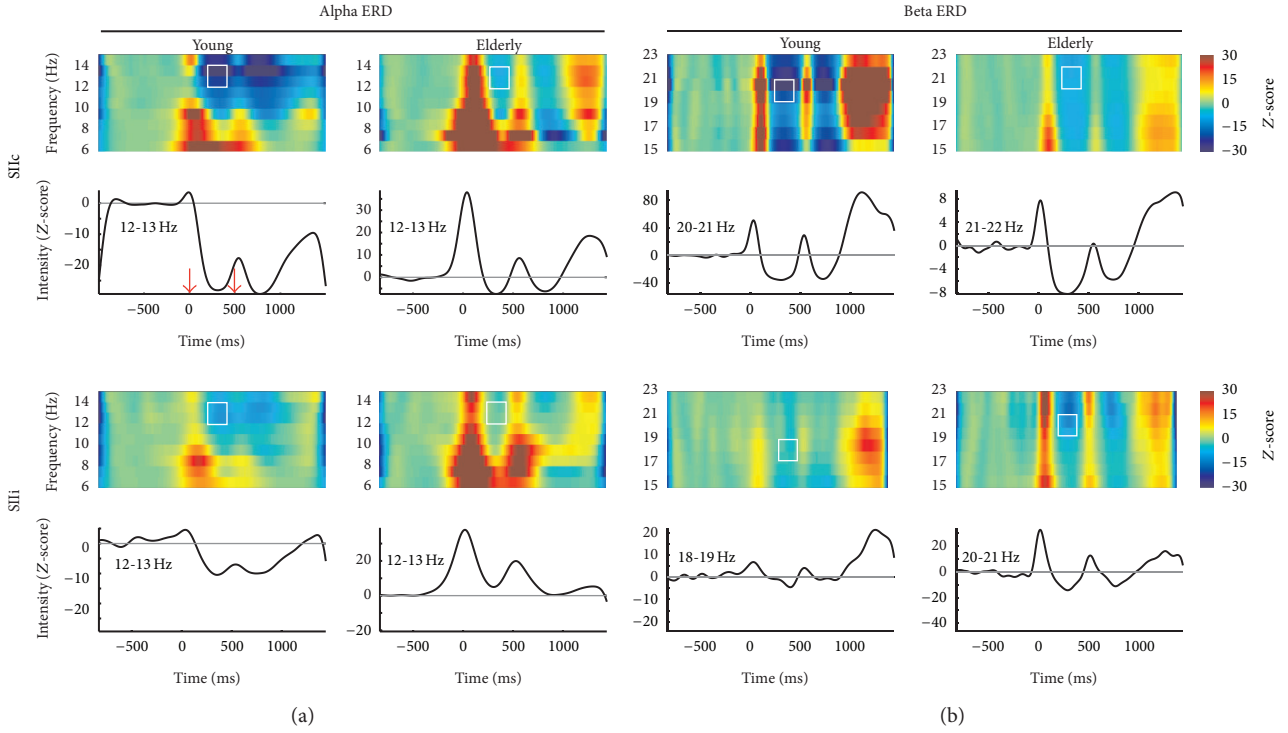



FIGURE 3: Time-frequency power analysis of the SIIc and SIIi for the alpha (a) and beta (b) frequency bands. The spectrograms between 6 and 14 Hz within alpha range and between 15 and 23 Hz within beta range are displayed. The plots below each time-frequency map exhibit the grand-averaged time course of event-related desynchronization (ERD) reactivity in the most reactive frequency bands (2 Hz) with respect to baseline power. The red arrows correspond to the onset of electrical stimulation. The peak values of induced ERD following stimulus 1 (white squares) are extracted for the subsequent analysis.

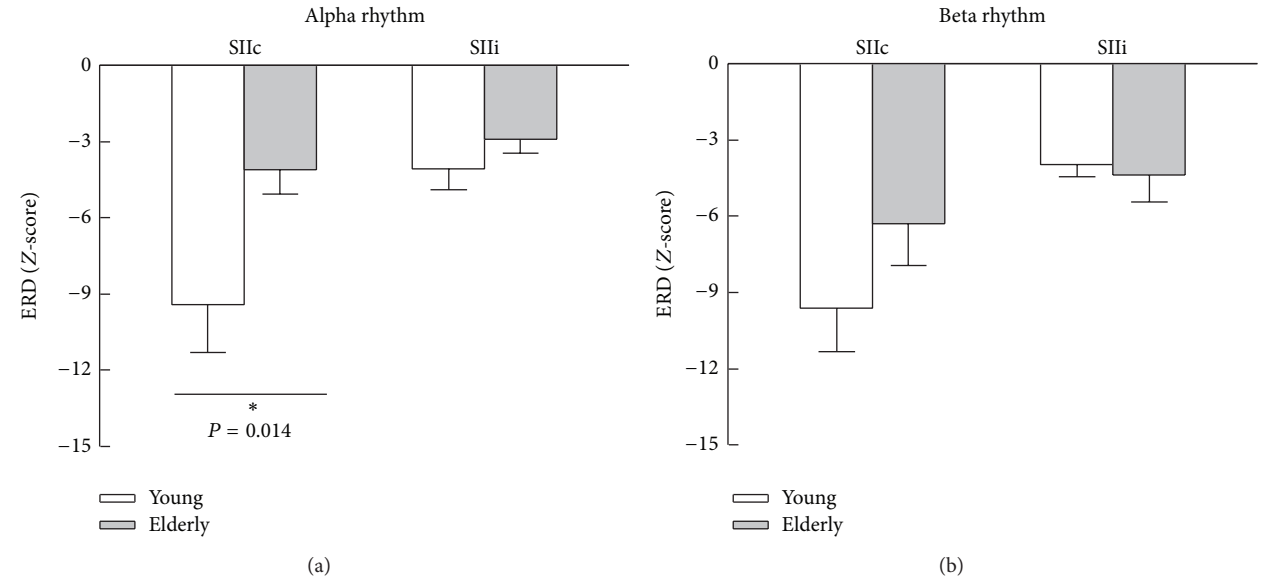



Figure 4: Mean values of stimulus 1-induced ERD peaks for alpha and beta rhythms. The bar above each column indicates the SEM.

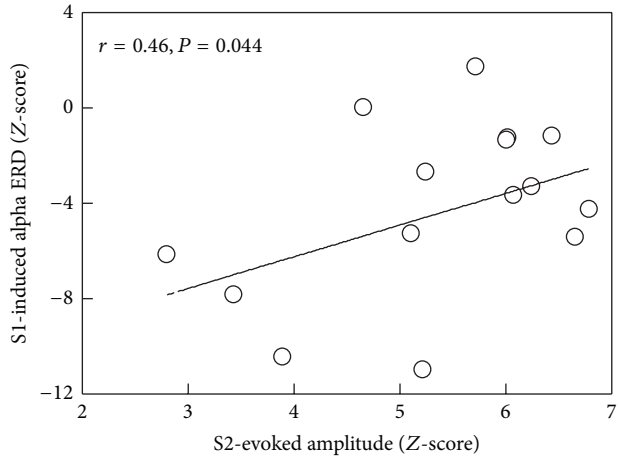



Figure 5: Association between stimulus 1- (S1-) induced alpha ERD and stimulus 2- (S2-) evoked response in the SIIc among the elderly participants.

changes in somatosensory alpha and beta oscillations. Our results demonstrated that the elderly showed reduced alpha ERD power in the SIIc. This significant finding particularly specific to alpha component indicated that this frequency band is strongly related to the function of the somatosensory cortex and has an apparent influence on information processing of the human brain [50]. The spontaneous alpha oscillatory activity could be replaced by a desynchronized activity following exogenous stimuli, such as median nerve stimulation [51]. In the present research, the desynchronized alpha rhythms might shift their role from idling activity to the processing of sensory inputs, likely through the mechanisms of changes in the local neural interactions [25, 52]. From this standpoint, we speculated that attenuation of alpha ERD in the aged adults was likely due to the age-associated decline of somatosensory information processing. One might argue that alpha ERD could be modulated by stimulus intensity [28]. However, due to the similar electric stimulus intensity provided to the young and elderly groups ($4.4 \pm 0.1$ mA versus $4.6 \pm 0.1$ mA), the age-related cortical power differences are unlikely to be a consequence of differential stimulus condition.

The underlying mechanisms regarding the association between event-induced neural oscillations and event-evoked responses remain unclear. Previous studies have independently investigated stimulus-induced ERD or stimulus-evoked activity by using paired-pulse somatosensory stimulation [17, 29, 53, 54]. Our present research attempted to relate S1-induced suppression of alpha rhythm to S2-evoked cortical excitability. It is conceptualized that more alpha suppression refers to better functioning of information processes; on the other hand, an increased response to the second stimulation within paired-pulse paradigms indicates an insufficient gating ability. We found that more S1-induced desynchronization of alpha oscillation, especially in SIIc, was associated with less S2-evoked amplitude of evoked response in the older adults. This observation suggests that oscillatory activities could, to some extent, account for the age-related decline of somatosensory SG.

Up to the present, it is extremely unclear why the association between S1-induced alpha ERD and S2-evoked amplitude was observed only in the SIIc region. One possible account is that, compared to the SIIc, SIIi signals usually showed poorer signal-to-noise ratios. Another interpretation is from the neuroanatomical and functional neuroimaging evidence. It has been suggested that SIIc and SIIi receive parallel projections from thalamus [43], which accounts for the reason that bilateral SII regions were venerable to aging, whereas the SI was relatively preserved. However, the mechanisms of ERD generation are more complicated by which reciprocal interactions between thalamus and somatosensory

cortices are involved. In the present study, the observed association between S1-indiced ERD and S2-evoked amplitude was restricted in the SII area. This finding did not imply that unilateral decreased S1-induced ERD modulated bilateral S2-evoked excitability. Here, we proposed a relation between age-related somatosensory induced and evoked responses, particularly in the SIIc region. It merits further investigation to determine other mechanisms underlying the age-related reduction of somatosensory SG.

Various neurophysiological studies have supported the argument that GABAergic inhibitory dysfunction is involved in physiological aging [55, 56]. For example, it has been shown that the age-related GABAergic degradation in the hippocampus was due to a selective loss of GABAergic interneurons [57, 58]. In humans, by intravenous injection of scopolamine, a cholinergic antagonist, the participants exhibited increased amplitudes of P50m during repetitive auditory inputs [59]. Moreover, the inhibition of somatosensory activation, particularly P35m in SI and bilateral SII regions, was modulated by GABAergic agonist lorazepam [60], suggesting the GABAergic regulation is related to inhibitory processing. Although our investigation at a system level was unable to verify the molecular mechanisms in terms of age-related defects of alpha ERD and SG, the current data extended the previous findings to highlight GABAergic alternations in human somatosensory information processing.

## 5. Conclusions

By using MEG and paired-pulse electrical stimulation to examine the time-frequency characteristics of somatosensory cortical processing, our results revealed age-related decline of SG and alpha ERD. Notably, an association between neural oscillations and evoked cortical excitability was found in the SIIc region, which indicated that lower S1-induced alpha ERD may be related to higher S2-evoked amplitude (insufficient gating). Taken together, these results suggest that the age-related decrease of somatosensory SG is related to the altered oscillatory activity. This paired-pulse protocol may also serve as an objective measure to assess the effects of training or intervention on somatosensory functioning in terms of cortical neural filtering ability in rehabilitation settings.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

## Authors' Contribution

Chia-Hsiung Cheng and Pei-Ying S. Chan contributed equally to this work.

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