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Research article

# Relationship between theta-phase gamma-amplitude coupling and attention-deficit/hyperactivity behavior in children

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## HIGHLIGHTS

- Theta-phase gamma-amplitude coupling (TGC) was analyzed as measured by scalp EEG.
- The Continuous Performance Test (CPT) and EEG were performed.
- An instantaneous phase method proposed by Cohen was used.
- Significant negative partial correlations between TGC and the CPT.
- TGC is a promising neurophysiological marker for ADHD behavior in children.

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## ABSTRACT

The Continuous Performance Test (CPT) is a valuable tool for assessing behavior in attention-deficit/hyperactivity disorder (ADHD). Quantitative electroencephalography (QEEG) is a promising tool for the diagnosis of ADHD. Recently, theta-phase gamma-amplitude coupling (TGC) measurement has received attention because it is a feasible method of assessing brain function. We investigated the relationship between CPT performance and EEG measures such as TGC and theta and gamma activity. EEGs were recorded from 68 volunteers from a camp for hyperactive children using a 19-electrode system. Their TGC, theta and 40 Hz gamma activity were estimated and compared with results obtained on the Korean ADHD Rating Scale (KARS) and the Intermediate Visual and Auditory (IVA) CPT. The results demonstrated significant negative partial correlations between TGC and the IVA CPT, such as the Response Control Quotient (RCQ) and Attention Quotient (AQ). TGC successfully identified the level of dysfunctional interaction of the attention/arousal system at a multi-scale large network level. It is thought that as the TGC increases, the efficacy of the system is very low or dysfunctional. Compensatory hyper-arousal patterns of the dysfunctional attention/arousal system may account for this effect. TGC is a promising neurophysiological marker for ADHD behavior in children.



## 1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a behavioral disorder characterized by pervasive symptoms of hyperactivity, impulsivity, and inattention. Inattention is not only a character in children with ADHD but also common character in other neurodevelopmental disorder such as dyslexia [17,20,50] and autism spectrum disorder [43]. But the types of attention deficit have various features according to specific disorders. At first, rapid orienting of visual attention before the correct letter-to-speech sound integration and a deficit in visuo-spatial attention have been suggested as the attentional causes of dyslexia [17,50]. And the children with autism spectrum disorder demonstrated deficits in the attentional disengagement, rapid attentional orienting and alerting [43]. While, the children with ADHD demonstrated deficits in the alerting and conflict attention networks but had normal function of

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the orienting networks [24]. The alerting network is believed to be involved in acquiring and maintaining an alert state. The orienting network involves the selection of information from sensory input for selective processing, while the conflict network entails the resolution of the conflict that arises between competing stimuli. These features of ADHD affect a child's academic performance, social competence, occupational choices and personality formation, and its negative impacts extend into adulthood [1,13]. Recently, ADHD has become a growing concern; the disorder requires treatment to reduce its persistence into adulthood [26]. However, it is not easy to diagnose children with ADHD. There is no single test for this purpose.

In the diagnosis of ADHD, the continuous performance task (CPT) has been recognized as a valuable tool that is capable of discriminating children with ADHD from normally developing peers [11,16,19,49]. According to previous reports, children with ADHD make more errors of commission and omission than normal controls on the CPT [33]. The CPT has been cited as the most frequently used measure of attention that involves cortico-subcortical interaction. Therefore, it is believed that the CPT demonstrates sensitivity to dysfunctions of the attention/arousal system [42].

The electrophysiological literature regarding attention commonly reports that enhanced gamma activity is associated with greater attention and precedes correct responses in a target detection task. Similarly, decreased gamma activity is associated with drowsiness and poor performance in the same task situation [34]. It has also been suggested that gamma activity and gamma synchrony are augmented by selective attention, potentially to enhance the perception and representation of relevant stimuli [32,47]. Gamma activity disturbance has been observed in ADHD. It has been reported that there is increased early gamma activity in children with unmedicated ADHD [51]. It has also been suggested that ADHD may be associated with abnormal enhancements of arousal responses to sensory stimuli, and/or an abnormal pattern of habituation produced by over-reactivity to novel sensory stimuli [51]. Among the various ranges of gamma bands, bands near 40 Hz gamma have received much attention for their contribution to the binding of diverse information into a single coherent percept and movement synchronization [18].

Johnstone et al. reviewed the event-related potential (ERP) literature in relation to attention-deficit/hyperactivity disorder (AD/HD) over the years 2002–2012 and offered potential to improve understanding of the specific brain dysfunction in children with ADHD [25]. But the present study was focused on the resting state of patient. Marcus Raichle et al. first used the term 'default-mode network (DMN)' to explain resting state brain function. The concept of a DMN provides an explanation for the consistent pattern of deactivation across a network of brain regions [39]. Therefore, the aim of the present study was to determine whether CPT performance is correlated with gamma synchrony to the theta phase during a resting state in children with high-risk ADHD. Recent studies of the human neocortex have demonstrated that the power of fast oscillations (30–150 Hz) is modulated by the phase of slow oscillations (1–8 Hz) [7,22]. We hypothesized that poor performance on the CPT would be associated with abnormal theta-phase 40 Hz gamma-amplitude coupling (40 Hz TGC).

## 2. Materials and methods

### 2.1. Subjects

Sixty-eight children and their parents visited the Gongju National Hospital (Gongju, South Korea) hoping to attend the 'Touch-Brain Camp for hyperactive children' in June 2010 and June 2011. To participate in the camp, each child was screened with the CPT and quantitative electroencephalography (QEEG) to assess the severity of their ADHD symptoms. Using the results of screening tests, twenty children were selected each year for the Touch-Brain Camp. In the present study, we used the results of the screening tests of volunteers enrolled in the Touch-Brain Camp. The initial report of the CPT and EEG data of volunteers were reviewed retrospectively. This study was approved by the Institutional Review Board (IRB) of the Gongju National Hospital (Gongju, South Korea) and was performed in accordance with the Declaration of Helsinki (World Medical Association: Ethical Principles for Medical Research Involving Human Subjects, 1964). All medical records of volunteers were treated anonymously, according to the recommendations of the IRB.

### 2.2. Korean ADHD rating scale (KARS)

For screening purposes, the 18-item Korean version of the ADHD Rating Scale(KARS) was used to assess ADHD behavior [45]. The KARS is a standardized screening tool for ADHD in Korean children [27,28]. The KARS is a rating scale completed by the parents of children with ADHD. We used the total KARS score as the one of measures of ADHD behavior.

### 2.3. Continuous Performance Test (CPT)

For screening purposes, the CPT was used to assess the level of functioning of the attention/arousal system. We used the Intermediate Visual and Auditory Continuous Performance Test (IVA CPT, BrainTrain, Inc., Richmond, VA, USA. www.braintrain.com) to obtain behavioral measures of attention [44]. The IVA CPT results yielded standardized scores of attention and the Response Control Quotient for each visual and auditory stimulus based on normative data. We used the full scale Attention Quotient (AQ) and Response Control Quotient (RCQ) of the IVA CPT to measure attention.

### 2.4. EEG recording and preprocessing

EEG recordings were obtained from the scalps of the volunteers using a Neuroscan SynAmps$^2$ DC-amplifier (Compumedics, North Carolina, USA). Four minutes of eyes-closed EEGs were recorded from 19 electrode sites (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2) based on the standard international 10/20 system at a sampling rate of 1000 Hz. We used the linked mastoid as the reference site. The impedance of each electrode was maintained below 15 kOhm throughout the EEG recording session.

We used MATLAB 7.0.1 (MathWorks, Massachusetts, U.S.A.) and the EEGLAB toolbox [15] to pre-process and analyze the EEG recordings. First, the EEG data were downsampled to 250 Hz. Next, the EEG data were detrended and mean-subtracted to remove the DC component. A 1 Hz high-pass filter and a 60 Hz notch filter were applied to remove eye and electrical noise. An independent component analysis (ICA) was performed to eliminate eye-blink and muscle artifacts. For the analysis, at least two minutes of artifact-free EEG data were selected from the four-minute recording of each subject based on visual inspection by clinical psychiatrists and EEG experts.

### 2.5. Power spectrum analysis

Two frequency bands were defined for spectral analyses: theta (4–8 Hz) and gamma (39–41 Hz). We investigated the power spectra of the EEG data for each subject using the short-time Fourier transform 'spectrogram.m' function of the signal processing toolbox in MATLAB. Time windows of 1000 ms with an 800-ms overlap and the Hamming window were used for the spectral analysis. Outliers that were far from the spectral value distribution of each