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Increased Frontomotor Oscillations During Tic Suppression in Children With Tourette Syndrome

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Abstract

This work investigated whether Tourette syndrome patients exhibit alterations in neural oscillations during spontaneous expression and suppression of tics. Electroencephalograms (EEGs) were recorded from 9 medication-naïve children with Tourette syndrome and 10 age-matched healthy subjects in resting conditions and during tic suppression. Their cortical oscillations were examined using the power spectral method and partial directed coherence. The authors found increased oscillations of broad frequency bands in the frontomotor regions of patients during tic expression, suggesting the involvement of aberrant cortical oscillations in Tourette syndrome. More significantly, prominent increases in theta oscillation in the prefrontal area and directed frontomotor interactions in the theta and beta bands were observed during tic suppression. Furthermore, the directed EEG interaction from the frontal to motor regions was positively correlated with the severity of tic symptoms. These findings suggest that the frontal to motor interaction of cortical oscillations plays a significant role in tic suppression.

Keywords

Tourette syndrome, tic suppression, neural oscillation, EEG, partial directed coherence

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Tourette syndrome is a neurobehavioral disorder characterized by tics, which are rapid, involuntary, and repetitive muscle contractions that produce stereotyped movements (motor tics) or sounds (vocal tics). Tics begin during childhood and persist for more than one year, worsening during the preadolescent years, and typically decline in severity and frequency by late adolescence.[1,2] Tics commonly increase under stressful conditions including the death of a parent, personal illness, beginning school, and parental separation and decrease when the individual with Tourette syndrome concentrates on certain tasks.[3,4] Despite the high estimated prevalence of Tourette syndrome of approximately 0.3%,[5] little is known about the neurophysiological mechanism underlying the generation and suppression of tics.

Previous anatomical and functional imaging studies have suggested that impaired cortico-striato-thalamo-cortical circuits, particularly frontostriatal dysfunctions, are involved in tic generation and suppression in Tourette syndrome.[1,6-8] These complex neural circuits encompass the primary sensorimotor, premotor, supplementary motor, prefrontal cortices, the basal ganglia, and thalamus. These circuits influence habit formation and procedural learning processes.[9-11] In particular, voluntary tic suppression entails the deactivation of the putamen, globus pallidus, and the thalamus combined with partial activation of the prefrontal cortex and caudate nucleus.[12] The degree of deactivation in the lentiform nucleus and thalamus was inversely correlated with the severity of the tics. A recent electroencephalogram (EEG) study showed that frontomesial coherence

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became elevated during both adaptive and compensatory acute tic suppression.[13]

Neural oscillations and synchronizations have been shown to underlie a variety of cognitive processes and behaviors such as attention, perception, cognition, and movement.[14-16] Indeed, abnormal rhythmic oscillations have been observed in many neuropsychiatric disorders including epilepsy, Parkinson disease, schizophrenia, and autism.[17,18] Aberrant neural oscillations have recently been suggested to play a role in the pathogenesis of Tourette syndrome.[17,19] According to this hypothesis, disturbed modulation of the basal ganglia by the prefrontal cortex produces aberrant neural oscillations in the basal ganglia and thus transient thalamocortical dysrhythmia, which can lead to a loss of control of sensory information and motor action.

The aim of the current study was to test the aforementioned hypothesis by investigating the possible alterations in neural oscillations during the spontaneous expression and suppression of tics in Tourette syndrome compared with those of healthy subjects at rest. The authors used a power spectrum to estimate the regional variations in each of the frequency bands in EEG rhythms during the spontaneous expression and suppression of tics in Tourette syndrome. To investigate the propagation and interactions of neural oscillations among cortical regions, the authors estimated partial directed coherence, which is a new approach that not only measures the flow of information between time series but also the direction of these interactions.[20] This approach uses a frequency-domain counterpart of the Granger causality using autoregressive modeling and captures the directions of interactions (or the transfer of information) of neural oscillations between 2 regions.[21-23] Thus, partial directed coherence analysis estimates the strength of the causal relationship between 2 oscillations in different cortical regions.[24] Recent studies have successfully used this analysis to investigate the coherence between certain cortical regions.[20] Evaluating partial directed coherence during human object recognition tests revealed widespread reciprocal information flow only during familiar object processing.[25] Babiloni et al examined the cortical activity during the visualization of standard commercial spots and estimated the pattern of cortical connectivity.[26] In major depressive disorder patients, lower frontal cortical interdependence was observed during resting and mental arithmetic tasks,[27] and lower frontal partial directed coherence values were seen during the recognition of facial expressions.[28] These studies suggest that the combined EEG analysis of power spectrum and partial directed coherence can determine the neural oscillations driving the response systems in the cortical network.[29,30] Therefore, the authors aimed to study the functional role of aberrant neural oscillations during the generation and suppression of tics.

Methods

Subjects

This study recruited 36 children with Tourette syndrome diagnosed based on the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition)[31] through the Department of Child and Adolescent Psychiatry at Hallym University Sacred Heart Hospital (Anyang-si, Kyungki-do, South Korea). All subjects were outpatients living near Seoul and Kyungki-do. Among these patients, the authors selected 9 medication-naïve male children (mean age $\pm$ SD: 9.67 $\pm$ 1.32 years; age range: 8-12 years; all right-handed) for this analysis based on the inclusion and exclusion criteria. The psychiatric diagnosis of these subjects was performed by a trained child and adolescent psychiatrist (HJ Hong) using the Kiddie-Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version–Korean Version, which are reliable and valid diagnostic instruments for child nd adolescent psychiatric diagnosis.[32] The Yale Global Tic Severity Scale[33] was used to rate the current and worst ever severity of tics and their comorbid psychopathologies and IQ were assessed by the Child Behavior Checklist[34] and the Korean Wechsler Intelligence Scale for Children–III.[35] Exclusion criteria comprised female, under 8 years old or above 12 years old, current or past exposure to any psychiatric medication, left-handedness, significant physical illness, a history of seizures or other neurological disorders or head trauma with a loss of consciousness, any epileptic form alteration in their EEGs, developmental delays, any concurrent psychiatric disorders other than attention-deficit/hyperactivity disorder (ADHD), and an IQ below 80. In addition, the authors excluded 2 Tourette syndrome subjects who showed an inability to suppress their tics during voluntary tic suppression and 4 subjects who had notable tics in the head or neck that could cause substantial head movements during subjects' screenings. Hence, all 9 Tourette syndrome patients suffered from multiple or single motor and/or phonic tics in their diverse muscle groups but typically had simple tics in the facial area (see Table 1 for more demographic data on the subjects). Written consent forms were received from all participants and their parents after the purpose and process of the study were clearly explained. This study was approved by the Institutional Review Board/Ethics Committee of Hallym University Sacred Heart Hospital in Korea.

The control group consisted of 10 age-matched healthy male children (average age, 9.50 $\pm$ 1.51 years; age range: 8-12 years, right-handed). The control subjects were recruited through advertisements posted on the notice board of Hallym University Sacred Heart Hospital's Web site. These subjects were unrelated to the patients, had no person history of movement disorders, had not been exposed to any psychiatric medications, and did not have any present or past axis I or axis II psychiatric diagnosis. These subjects also underwent the comprehensive psychiatric assessments including the Kiddie-Schedule for Affective Disorders and Schizophrenia–Present and Lifetime Version–Korean Version,[32] the Child Behavior Checklist,[34] and the Korean Wechsler Intelligence Scale for Children–III[35] and the same exclusion criteria checklist as Tourette syndrome subjects. All participants and their parents provided informed written consent after the purpose of the study and its processes were explained.

EEG Recording and Preprocessing

The EEGs were recorded from the 19 scalp loci of the international 10-20 system with all electrodes referenced to Cz using digital EEG equipment (Cadwell Inc, Washington) in a quiet room. Tourette syndrome subjects were comfortably laid in bed for 5 minutes during their periods of spontaneous tic expression. To minimize the artifacts in the EEG patterns of Tourette syndrome patients by tics or other movements, a custom-made "head fixation device" was developed. The subject's forehead and jaw were tightly fixed with straps during EEG recording using a head fixation device developed in the lab (Figure S1). In this relaxed state, the authors recorded the EEGs of Tourette syndrome patients for 5 minutes with their eyes closed in resting or tic generation conditions. Then, for the next 5 minutes, the

Table 1. Demographic and Clinical Profiles of Tourette Syndrome and Healthy Children.

	Tourette Syndrome Patients (N = 9)	Healthy Subjects (N = 10)	*P* Value
Age	99.67 (1.32)[a]	99.50 (1.51)	.802
Wechsler Intelligence			
Verbal IQ	1116.44 (33.36)	1110.40 (12.95)	.602
Performance IQ	1101.89 (9.56)	1101.30 (24.65)	.915
Total IQ	1104.33 (10.81)	1107.10 (12.74)	.619
Yale Global Tic Severity Scale score			
Motor tic score	114.56 (2.17)		
Phonic tic score	114.56 (5.98)		
Disability	330.00 (6.36)		
Total score	553.89 (15.46)		
Onset age	66.78 (2.17)		
Comorbidity			
None	77		
ADHD	22		
Child Behavior Checklist subscale			
Withdrawal	449.22 (8.99)	448.00 (4.81)	.894
Somatic complaint*	553.22 (12.42)	443.40 (4.09)	.030
Depression/anxiety*	555.89 (11.50)	443.00 (6.63)	.020
Immaturity	553.11 (10.76)	446.10 (7.39)	.113
Thought problem*	557.89 (12.67)	446.20 (3.80)	.012
Attentional problem*	556.56 (10.45)	441.09 (8.98)	.003
Delinquent behavior	448.54 (10.19)	446.60 (7.72)	.218
Aggressive behavior	551.56 (8.23)	446.60 (7.72)	.354
Internalizing symptoms*	552.56 (12.42)	442.70 (6.09)	.039
Externalizing symptoms	551.33 (7.66)	444.70 (7.20)	.068
Total score*	555.33 (8.14)	442.50 (7.32)	.0012

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; IQ, intelligence quotient.
[a]Standard deviations are reported in parentheses.
*Statistically significant.

authors recorded the EEGs of Tourette syndrome patients while they were instructed to voluntarily suppress their tics in the tic suppression condition.

The state of tic suppression was defined using the following 2 conditions: (1) the frequency of tic occurrences was lower during periods of tic suppression compared to a subject's resting state and (2) there was a time interval of at least 30 seconds between successive tic occurrences. To determine the exact timing of the EEGs and their relationship to tic generation, the authors monitored the electromyography with a sampling frequency of 200 Hz using electrodes attached to the parts of the face where these tics happened. All processes were recorded using a high-resolution (25 frames/sec) videotape recorder (Sony, Japan). Similarly, healthy subjects were asked to lie comfortably in bed, and the EEGs of the subjects in the head-fixation device were recorded with their eyes closed for 5 minutes.

EEGs sampled at 200 Hz were digitally filtered with a low cutoff frequency at 0.53 Hz and a high cutoff frequency at 70 Hz. The authors used 3 epochs of 10 seconds for each subject and the mean estimate of 3 epochs for any measure was used. For EEGs in the tic suppression state, the authors extracted EEG epochs recorded when Tourette syndrome subjects exhibited no tics in the tic suppression condition. To reduce the presence of artifacts in the EEG patterns of Tourette syndrome patients from tics and related movements, the authors applied independent component analysis. This method attempts to identify the independent sources of the observed signals by minimizing the mutual information among the different sources.[36] The authors used the Infomax algorithm and default parameters as implemented in the *runica* function of the EEGLAB toolbox.[37] The independent component analysis was performed on all subjects and conditions to obtain robust spatiotemporal activity patterns.[38]

Data Analysis

The power spectral density function of the EEG was obtained by the Fourier transform of the autocorrelation sequence of EEGs scaled by an appropriate constant through the fast Fourier transform algorithm. The Welch method was used as a nonparametric method for estimating power spectral density with the Hamming window function (8 windows with 50% overlap).[39] The absolute power spectrum was estimated for each channel in each of the frequency bands based on the definitions of the delta (0.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-13.5 Hz), beta (13.5-29.5 Hz), and gamma (29.5-70 Hz) bands.

Partial directed coherence was applied to analyze EEGs and the viability of this method was validated.[23,40-42] BioSig (http://biosig.sf.net), an open-source software library for biomedical signals, was used to perform autoregressive modeling and partial directed coherence analysis. Partial directed coherence is normalized with respect to the total influx of information, and it has no value when there is no direct information transfer between time series.

Statistical Analysis

For demographic data, an independent-sample *t* test was used after Levene's test for the equality of variances. Corrections for the inequality of variances were performed whenever necessary. To identify

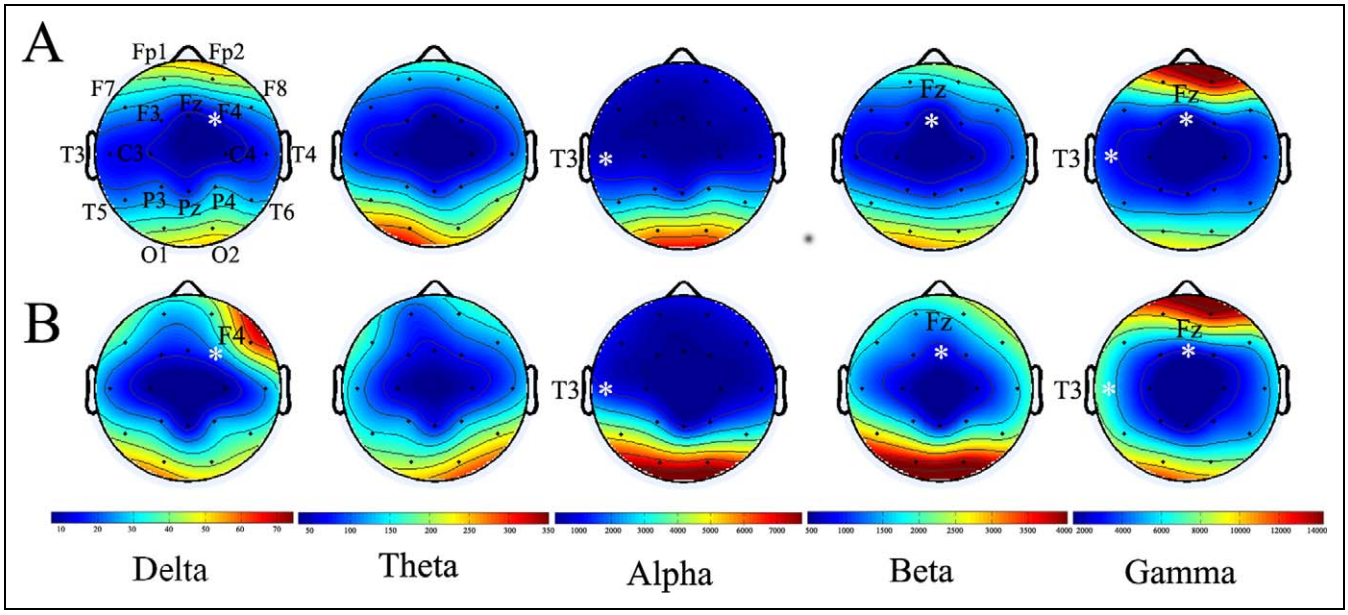

Figure 1. Power spectra of electroencephalograms (EEGs) in (A) healthy and (B) Tourette syndrome children in the resting condition. The white asterisks in (A) and (B) represent significant increases in spectral power in Tourette syndrome patients compared with healthy subjects ($P < .05$).

neural correlates of tic generation in Tourette syndrome, the authors compared the power spectrum and partial directed coherence of EEGs in Tourette syndrome patients and healthy controls during resting conditions and used an independent-sample t test with alpha = .05 for the power spectrum and .01 for partial directed coherence. For comparisons between spontaneous expression and suppression of tics in Tourette syndrome, paired-samples t tests were performed with the same statistical criteria. The authors also performed the Bonferroni correction for multiple comparison problems, but no significant differences were observed in this analysis. All statistical analyses were 2-sided and performed using SPSS for Windows, version 13.0 (SPSS Inc, IL., Chicago).

Pearson correlations were performed among power spectrum, partial directed coherence, and clinical characteristics of Tourette syndrome patients to assess the relationship between the severity of tics and the neural oscillations at certain channels or pairs of channels. The clinical variables included age, age of onset of Tourette syndrome, the Yale Global Tic Severity Scale scores, and subscales of the Child Behavior Checklist. P values < .01 were considered as significant.

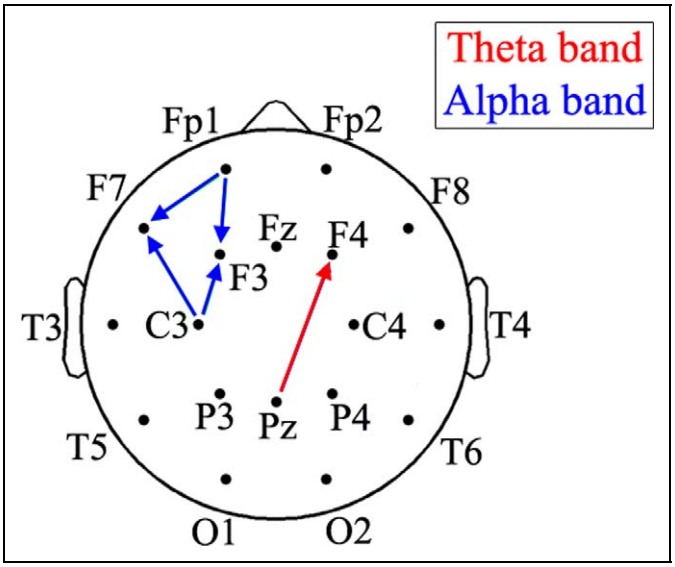

Figure 2. Topological difference map of the partial directed coherence values for electroencephalograms (EEGs) between healthy and Tourette syndrome children in the resting condition. The partial directed coherence values were significantly increased in Tourette syndrome patients compared with healthy subjects in the indicated pairs of channels ($P < .01$).

Results

Neural Oscillations During Spontaneous Expression of Tics

To determine the presence of aberrant neural oscillations during spontaneous expression of tics in Tourette syndrome patients, the authors estimated the power spectrum of EEG patterns in 9 medication-naïve Tourette syndrome children and 10 healthy children. Figure 1 illustrates the spectral power of each band in healthy subjects and Tourette syndrome patients in a resting condition. The authors found significant differences between the groups in the delta band at F4, $t(17) = -2.127$, $P = .048$, the alpha band at T3, $t(17) = -2.291$, $P = .035$, the beta band at Fz, $t(9.66) = -2.311$, $P = .044$, and the gamma band at Fz, $t(9.142) = -2.393$, $P = .040$, and T3, $t(12.912) = -2.504$, $P = .026$. In all channels with differences, the spectral power in Tourette syndrome patients increased compared to healthy subjects. This result indicates increased cortical oscillations of broad frequency bands in frontomotor areas during spontaneous tic expression.

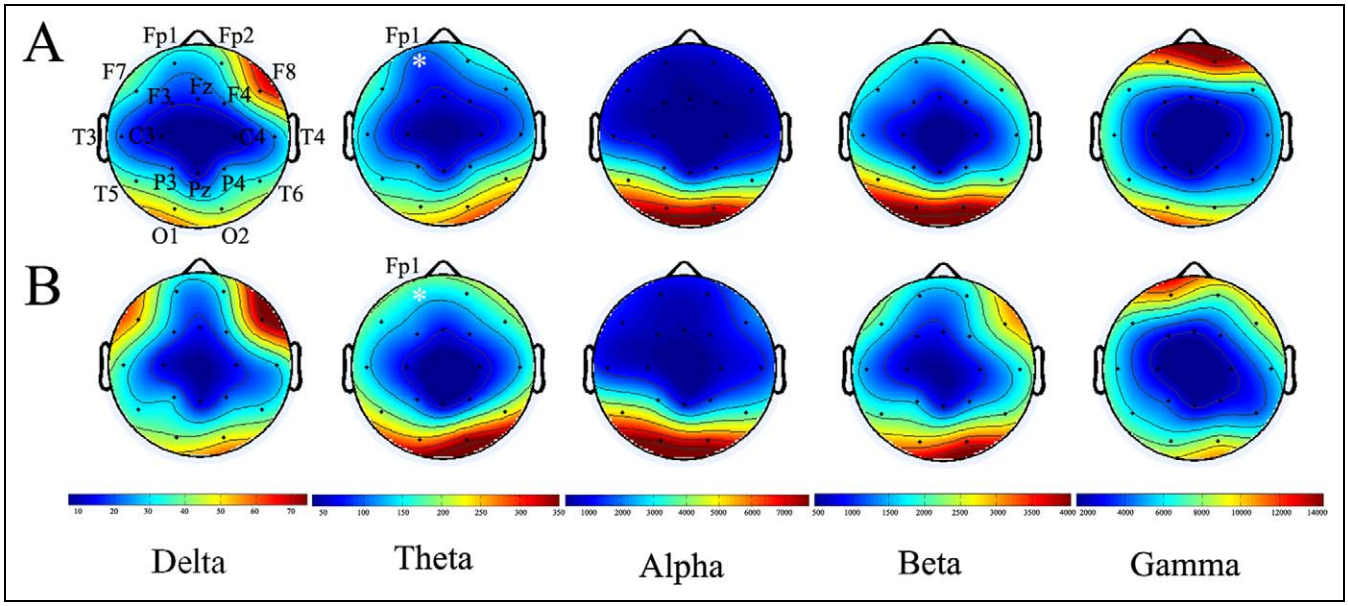

Figure 3. Power spectra of electroencephalograms (EEGs) in (A) healthy and (B) Tourette syndrome children in the tic suppression condition. The white asterisks in (A) and (B) represent significant increases in spectral powers at F7 in the delta band and Fp1 in the theta band in the tic suppression condition of Tourette syndrome patients compared with those at rest ($P < .05$).

To assess directional interactions of neural oscillations between different cortical regions during spontaneous expression of tics in Tourette syndrome patients, the authors estimated partial directed coherence values between all pairs of EEG patterns in 9 Tourette syndrome and 10 healthy children. Figure 2 presents the results of the partial directed coherence analysis. In the theta band, the partial directed coherence values from Pz to F4 in Tourette syndrome patients were larger than those in healthy subjects, $t(19) = -2.9479$, $P = .0083$. The partial directed coherence values in Tourette syndrome patients revealed a significant increase compared with those of the control group from C3 to F7, $t(19) = -3.0995$, $P = .0059$, from C3 to F3, $t(19) = -3.0486$, $P = .0066$, from Fp1 to F7, $t(19) = -3.0074$, $P = .0072$, and from Fp1 to F3, $t(19) = -2.9239$, $P = .0087$, in the alpha band. This result indicates that neural oscillation propagates from the left prefrontal and centroparietal regions to the left frontal regions, which could be associated with the generation of tics in Tourette syndrome.

The authors tested whether EEG measures in channels or pairs of channels that showed statistically significant differences between the 2 groups were correlated with the clinical factors of the Tourette syndrome patients. The clinical factors analyzed here included age, age of onset of Tourette syndrome, the duration of illness, the Yale Global Tic Severity Scale scores, and the Child Behavior Checklist Inattention subscale. The authors found no significant correlations between EEG abnormalities in the patient group and these clinical factors.

Neural Oscillations During Tic Suppression

To investigate alterations in neural oscillations during the suppression of tics in Tourette syndrome patients, the authors compared the power spectrum of EEG patterns in the Tourette syndrome and healthy children between conditions of spontaneous expression and suppression of tics. Figure 3 shows the differences in the spectral power of each band in Tourette syndrome patients between the 2 conditions. The authors found a significant increase in spectral power in the suppression condition in the theta band at Fp1, $t(8) = -3.181$, $P = .013$, compared with those observed during the rest periods (Figure 3). This result indicates that theta oscillations in the prefrontal region are associated with the voluntary suppression of tics.

Partial directed coherence analysis revealed that Tourette syndrome patients exhibited a significant increase in partial directed coherence values during tic suppression compared with during spontaneous expression from F3 to T4, $t(10) = -3.4411$, $P = .0063$, and from C3 to T4 in the theta band, $t(10) = -3.5455$, $P = .0053$. In the beta band, significant increases in the partial directed coherence values were observed from F3 to T3, $t(10) = -3.5257$, $P = .0055$, and from F8 to T3, $t(10) = -3.2607$, $P = .0086$, as shown in Figure 4. These results indicate that neuronal interactions directed contralaterally from the frontal areas to the motor regions are involved in tic suppressions within the theta and beta bands.

The authors investigated the correlations between these EEG measures during tic suppression and the clinical characteristics of Tourette syndrome patients. This analysis revealed significant correlations between the Yale Global Tic Severity Scale motor tic scores and the partial directed coherence values from F3 to T4 in the theta band (Figure 5). This result indicates that the frontomotor interactions increased in Tourette syndrome patients with more severe symptoms observed during tic suppression.

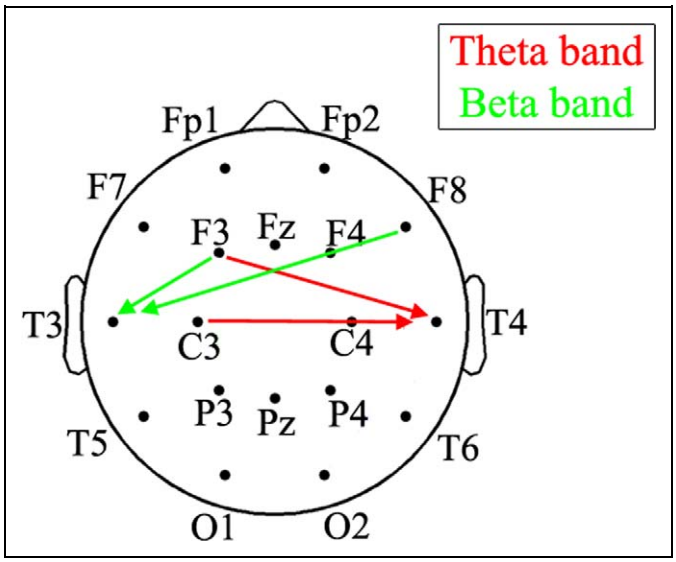

Figure 4. Topological difference map of the partial directed coherence values for electroencephalograms (EEGs) of Tourette syndrome patients between the resting and tic suppression conditions. The partial directed coherence values of Tourette syndrome patients were significantly increased in the suppression condition, compared to those in the resting condition ($P < .01$).

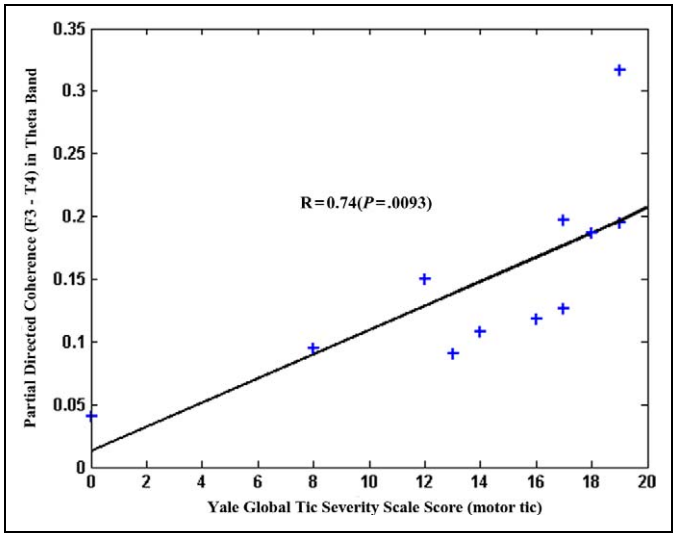

Figure 5. Correlation between the Yale Global Tic Severity Scale Score motor tic scores and the partial directed coherence values from F3 to T4 in the theta band in Tourette syndrome patients during tic suppression ($R = 0.74$, $P = .0093$).

Discussion

The authors investigated the possible involvement of aberrant neural oscillations during the spontaneous expression and suppression of tics in Tourette syndrome. Power spectrum analysis of the EEG in 9 medication-naïve Tourette syndrome children and 10 healthy children revealed increased oscillations of broad frequency bands in the frontomotor regions. This finding suggests the involvement of aberrant cortical oscillations in the pathophysiology of Tourette syndrome. Partial directed coherence showed significant increases in theta oscillation in the prefrontal area and directed frontomotor interactions in the theta and beta bands during tic suppression, and these findings were positively correlated with the severity of the tic symptoms. This finding suggests that the frontomotor interaction of cortical oscillations plays a significant role in both the generation and suppression of tics in Tourette syndrome children.

When Tourette syndrome children were allowed to spontaneously express their tics at rest, they showed prominent increases in the alpha band from the left prefrontal and central to the left frontal regions and in the theta band from the parietal to the right frontal regions. Although EEG has a poor spatial resolution and the possible topographic implications of this finding must be interpreted with extreme caution, these areas are largely consistent with previously detected areas that were associated with tic generation and premonitory urges.

Numerous neurophysiological studies in Tourette syndrome have suggested altered neuronal activity in motor or promoter circuits that may be associated with the abnormal organization of movement control.[43-50] A recent fMRI study suggested an abnormal activation pattern of the motor cortex during voluntary movement and suppression of voluntary movement in Tourette syndrome.[51,52] The observed increases in broad-band oscillations in the frontomotor regions are consistent with altered neuronal activity in motor circuits in Tourette syndrome.

The onset of motor or vocal tics was associated with activation in sensorimotor areas including bilateral activation of the superiorparietal lobules and the cerebellum.[11] These results suggest that fast neural oscillations were observed before tic onset and premonitory urges in the central frontal and left temporal regions, particularly in the anterior cingulate and insular cortex.[11,53] The supplementary motor area in the area of the sensory premonitory urges was activated before tics occurred. In addition, the increase in the theta partial directed coherence value from Pz to F4 and alpha partial directed coherence from C3 to F3 and F7 can reflect the onset of tics because these regions were associated with sensorimotor systems including the bilateral superior parietal lobule.[11] The presence of increased functional coupling from Pz to F4 is consistent with previous findings of positive correlations between the activities of the superior parietal lobe and the lateral premotor area.[54]

During voluntary tic suppression, The authors observed increased theta oscillation of the prefrontal region and increased theta and beta partial directed coherence values from the frontocentral to the temporal regions in children with Tourette syndrome. These enhanced frontomotor functional connections in the theta and beta bands, mainly from the frontal to the primary sensorimotor regions, are implicated as neural oscillations involved in the process of tic suppression. This possible modulation of motor areas by frontal regions is in accordance with previous studies reporting that activations at the right frontal cortex, right caudate nucleus, cingulate cortex, and temporal cortex as well as deactivations in the lentiform nucleus and thalamus were involved in tic suppressions of Tourette syndrome.[17,19,55]

A previous study conducted an MRI on adults with Tourette syndrome during tic suppressions and suggested elevated levels of coherence between the sensorimotor areas and the medial frontal cortex.[12] It also found the delta oscillation in F4 and the alpha interactions from Fp1 to F7 and F3. Other studies also reported activations in the dorsolateral prefrontal cortex in Tourette syndrome patients compared with normal controls.[13] Taken together with these findings, the results suggest that directed modulation from the prefrontal cortex, particularly the dorsolateral prefrontal cortex, inhibits the activity of the primary sensorimotor areas that are associated with tic generation.

A significant correlation was observed between the partial directed coherence value from F3 to T4 in the theta band and the severity of motor tics in this study. This implies that the functional interactions from the frontal to motor regions pertain to compensatory processes because Tourette syndrome patients with more severe symptoms are ineffective in exhibiting more enhanced coupling.[11,53] Consistent with this finding, increased prefrontal activations were associated with greater tic severity in previous functional imaging studies.[10,56,57] In addition, larger anatomical volumes of the dorsal prefrontal regions were reported in Tourette syndrome.[17,58] This hypertrophic dorsal prefrontal cortex in children with Tourette syndrome appears to evolve as an activity-dependent, hyper-excitable, neuroplastic response to the need to suppress tics.[59]

Note that the frontomotor interaction during tic suppression was directed contralaterally from the left or right frontal region to the right or left temporal region, respectively. Tourette syndrome patients have smaller structural volumes of the corpus callosum, and this volume is associated with tic severity.[60] White matter connectivity in the corpus callosum, measured by a fractional anisotropy index from diffusion tensor images, is also reduced in children with Tourette syndrome.[61] Thus, the finding of interhemispheric interactions during tic suppression supports the hypothesis that altered callosal connectivity through neuronal plasticity leads to exaggerated prefrontal excitability and thus attenuation of tic symptoms.

Because EEG predominantly reflects cortical oscillations, it is unclear whether subcortical abnormalities contribute to the aberrant neuronal oscillations found in this study.[62] Interestingly, the authors observed that theta oscillations play a role in both the expression and inhibition of tics. Tourette syndrome patients showed increased coherence from the centroparietal to the frontal areas and from the left frontocentral to the right temporal regions during the resting state. This frequency band coincides precisely with the periodic variations of thalamocortical dysrhythmia, which has been suggested to be related to the pathophysiology of Tourette syndrome.[17]

The theta and beta-band results of the study do not exactly coincide with those of a previous study demonstrating enhanced alpha coherence during acute tic suppression.[17] This discrepancy might stem from the different ages of the subjects or the differences in analysis procedures between the 2 studies. The mean age of the subjects was 9.67 years, while the previous study had subjects with a mean age of 28 years. Tourette syndrome typically improves by the end of the second decade of a person's life. Tourette syndrome in adults represents more severe pathological conditions and a different phenotype than Tourette syndrome in children. In the previous study, alpha coherence was only estimated among several frequency bands based on its levels of response to cognitive controls. However, only considering the alpha oscillations provides limited information about cortical interactions because there are negative correlations between the distances of oscillatory neural responses and their frequency. Thus, the analysis using the alpha band most likely limited the possible range of cortical interactions.[13] Because the delicate coordination of neural rhythmic activities entails an appropriate selection of oscillation frequencies and degrees of synchronization, broadband rhythmic activities and their cross-band interactions have to be taken into consideration for further investigations.[18]

The finding of aberrant neural oscillations during tic suppression is of substantial clinical relevance for Tourette syndrome. These noninvasive and quantitative measures using EEG can be tools for the diagnosis of Tourette syndrome and the monitoring of its progression and the effects of treatment, and could also represent a possible target of therapeutic intervention. The importance of tic suppression has been underscored by its potential use in the treatment of Tourette syndrome, such as behavioral training, neurofeedback, and neuromodulation therapy.[24] Transcranial magnetic stimulation, a process that is noninvasive, reversible, relatively localized, and safe, has shown promise in the treatment of various neuropsychiatric disorders including mood and anxiety disorders. Previous studies using transcranial magnetic stimulation reported aberrant motor inhibitory control in Tourette syndrome patients and studied the therapeutic effects of this stimulation.[63,64] Transcranial magnetic stimulation can have an effect on neural modulation by modifying spike timing and the phase relationships of neural signals.[65-68] Repetitive transcranial magnetic stimulation of the primary motor cortex in normal subjects was able to modulate activities in the basal ganglia, frontal, temporal cortex, and behavioral changes in sensorimotor functions.[69]

These findings must be interpreted in light of the limitations of this study. First, the study included 2 subjects with Tourette syndrome and comorbidities of ADHD and obsessive-compulsive disorder, which could affect the results. In addition, a small number of Tourette syndrome children were studied here, leading to the possibility of spurious findings. The decision to study only males limits the generalizability of the findings to males only. The directionality of partial directed coherence must be interpreted with caution because partial directed coherence is only capable of capturing the direction of information flow in terms of the Granger causality. It is difficult for this method to detect the exact anatomic location or the origin of the oscillatory EEG rhythms because of the ability of this method to convey volume and because of the considerable redundancies that result. Thus, the findings should be confirmed in the future using other imaging modalities such as magnetoencephalography.

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Author Contributions

HJH and JJ conceived the idea and designed the study. HJH, MKC, and KH conducted the experiments. HJH, HSS, MC, JO, and SK analyzed the data. HJH and JJ wrote the draft of the manuscript. HJH, HSS, JO, and JJ revised and completed the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

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Ethical Approval

Ethics approval was obtained by the Institutional Review Board/Ethics Committee of Hallym University Sacred Heart Hospital (2004) in Korea.

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