Analysis of EEG Coherence During Active Suppression in Patients with Tourette's Syndrome

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ANALYSIS OF EEG COHERENCE DURING ACTIVE SUPPRESSION IN
PATIENTS WITH TOURETTE’S SYNDROME

By
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A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of
the requirements of the Sally McDonnell Barksdale Honors College.

Oxford
May 2018

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Acknowledgements

Special thanks to my advisor, Dr. Waddell, for his guidance and patience throughout the process of completing this work. I would also like to thank my readers Dr. Gustafson and Dr. Morrison for their time and contributions. Big thanks also to Brittany Watson for helping me gather data and all the other work she contributed to help me complete this project. And finally, I would like to thank all my family and friends for their support and encouragement.
ABSTRACT:
ANALYSIS OF EEG COHERENCE DURING ACTIVE SUPPRESSION IN PATIENTS WITH TOURETTE’S SYNDROME

One of the first studies that investigated quantitative qualities of Tourette syndrome (TS) found that during active suppression of tics TS patients exhibit increased coherence in the alpha frequency (Serrien, Orth, Evans, Lees, & Brown, 2005). In this study, we attempted to validate the previous literature to allow for future research into the role played by increased coherence during active suppression. Our findings, however, showed that there was no significant increase in coherence between active suppression and rest. The findings in this study, along with previous literature, may suggest that TS patients with comorbid obsessive-compulsive disorder (OCD) affect the alpha power seen in these individuals. This finding shows that coherence may not increase in all TS patients as previously thought, but instead may increase only in individuals with pure TS. These findings show that further research, with a larger sample size, will be needed to determine the effects of comorbid OCD on the change in coherence during active suppression.
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1: INTRODUCTION

Tourette syndrome (TS) is a neurological disorder that is characterized by both motor and vocal tics (Robertson, 2000). The diagnosis for TS often occurs before the age of 21 and it is diagnosed using history and observation of both motor and phonic tics, and through the presence of comorbid behavioral disorders such as Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive-Compulsive Disorder (OCD) (Jankovic, 2001). The tics that characterize TS patients often begin between the ages of 3 and 8 and follow a waxing and waning pattern until 19 or 20 years old when the tic severity often reduces (James F. Leckman, 2002). There is no definitive laboratory test for TS, however, the Tourette Syndrome Diagnosis Group has created specific criteria to definitively diagnose TS, which includes a time line for diagnosis and characteristic manifestations of the disorder (Jankovic, 2001; James F. Leckman, 2002). Along with efforts to ensure proper diagnosis an effort has been made to accurately rate the severity of tics displayed in TS (J. F. Leckman et al., 1989).

The structural differences of the brain are one of the first places to look to better understand the characteristics of TS. The frontostriatal system has been singled out as one of the prime suspects for several disorders including TS, ADHD, and OCD (Bradshaw & Sheppard, 2000). Pathophysiologic studies of TS patients have displayed differences in the frontostriatal system from healthly individuals in several ways. Differences in the size of the basal ganglia have been shown in TS patients (J. F. Leckman, Knorr, Rasmusson, & Cohen; Peterson, Thomas, Kane, & et al., 2003). Specifically, a reduction
in the caudate nucleus within the basal ganglia has been shown in TS individuals and can be used to indicate the severity of both tics and OCD (Bloch, Leckman, Zhu, & Peterson, 2005; Peterson et al., 2003). Furthermore, it has been shown that an increase of white matter is often observed in the frontal lobe further implicating abnormality in the frontostriatal circuitry (Fredericksen et al., 2002).

The dopamine pathways within the frontostriatal circuit has also been cited as a potential difference that could explain the disorder (Wolf et al., 1996; Wong D et al., 1997). An increase in the density of receptors has been shown in certain subgroups of TS patients (Wong D et al., 1997). Also the binding affinity of D2 receptors in monozygotic twins has shown that it can predict severity of tics (Wolf et al., 1996). The possibility of the dopamine pathway being involved in the manifestations of TS has further been show due to the use of dopamine receptor blocking drugs as a treatment method (Jankovic, 2001).

TS is a genetically inheritable disorder however the exact inheritance is still debated (Pauls, 2003). There has been a search for the specific gene or genes that characterize the disorder, however, it is not yet known which specific gene causes the disorder, although there are several potential candidates (Hyde, Aaronson, Randolph, Rickler, & Weinberger, 1992; Pauls, 2003). Abnormalities on multiple chromosomes have been cited, however, incomplete understanding of the functions carried out by the genes of interest have made finding strong candidate genes difficult (Pauls, 2003). The gene CNTNAP2, which is believed to play a part in the Nodes of Ranvier, has been shown to be affected by a translocation in one family of TS individuals with OCD (Verkerk et al.,
The karyotypes of TS patients are mostly found normal so this particular anomaly is an unlikely genetic cause for all cases of TS (Robertson & Trimble, 1993). Further research is needed to show which gene or genes influence TS.

The influence of contextual factors plays a significant role in the characterization of TS. One common occurrence in TS patient are premonitory urges. Premonitory urges are sensory phenomenon that occur before a tic (WOODS, PIACENTINI, HIMLE, & CHANG, 2005). In one study 79% of participants experienced premonitory urges and 57% described the premonitory urges as more bothersome than the tics (Cohen & Leckman, 1992). The tics are often responses to relieve the premonitory urge (Cohen & Leckman, 1992). TS patients who also have OCD often describe a “Just Right” perception that they experience after doing a number of compulsions until they were “Just Right” (J. F. Leckman, Walker, Goodman, Pauls, & Cohen, 1994). This “Just Right” perception may play a similar role to the premonitory urge in TS individuals with comorbid OCD. The tics associated with TS are often influenced by outside stimuli. Stress and other anxiety provoking events exacerbate tics in TS individuals (Conelea & Woods, 2008). The effects of contextual factors play a part in the severity of TS.

TS individuals are capable of suppressing tics for short periods of time and it has been shown that this suppression may improve quality of life (Matsuda, Kono, Nonaka, Fujio, & Kano, 2016). Furthermore, it has been shown that the ability to suppress tics may be associated with the development of executive control (Yaniv et al., 2017). This shows that there may be some type of adaption seen in TS patients allowing them to successfully suppress tics.
Electroencephalography (EEG) has been used to show that there is an increase in coherence among certain neural connections in the alpha frequency band when TS individuals are asked to suppress their tics (Serrien et al., 2005). EEG is a noninvasive tool used to measure brain activity in various brain regions using electrodes positioned on the scalp. The electrodes receive signals from multiple firing neurons and combine all of these neuron signals into one complex wave. Coherence is the measure of the relationship between two signals, in this case the two signals are the signals coming from two different electrodes in the EEG cap. The more similar the frequency content of two signals the greater their coherence. Increased neural coherence has been shown to indicated an increase in brain connectivity (Bowyer, 2016). Increased coherence has also been shown to play a part in neural processes such as associative learning (Miltner, Braun, Arnold, Witte, & Taub, 1999). Coherence is calculated using the equation

$$|R_{ab}(\lambda)|^2 = |f_{ab}(\lambda)|^2 / f_{aa}(\lambda)f_{bb}(\lambda).$$

In this equation, the numerator indicates the cross spectral density between a and b and the denominator represents the auto spectral density for a and b respectively. Four connections were shown to have significantly increased coherence, F3-C3, F4-C4, FCz-C3, and FCz-C4 (Serrien et al., 2005). This could show a type of neural plasticity that develops in TS patients allowing them to better control their tics. Serrien’s study is one of the first studies to quantitatively examine the neural connections of TS patients. And further testing of this study could potentially help to find new ways to characterize TS and improve quality of life for TS patients.
2: METHODS

2.1 Data acquisition:

Five participants with TS gave informed consent by signing the Human IRB form and answering all related questions. The PUTS scale was then administered to the participants in a quiet room to access the severity of the premonitory urge. The PUTS scale was then followed by the EEG fitting. Continuous EEG was recorded using Ag-AgCl electrodes fitted using the International 10-20 standard of placement. The electrodes were in a 40 channel EEG cap (Compumedics, Charlotte, North Carolina) allowing for easier placement. Each electrode contained a dehydrated disc (Compumedics, Charlotte, North Carolina) that was rehydrated by injecting saline solution into the electrode with a blunt tip needle, which helped reduce impedance to less than five kilo-ohms. The signals were amplified and digitized (Compumedics, Charlotte, North Carolina) before being sent to acquisition software (Scan 4.3; Advanced Medical Equipment) that used a sampling rate of 250 Hz. The electrodes tested were the same electrodes found to have significant increases in coherence during active suppression in the previous literature, specifically F3, C3, F4, C4, and FCz (Serrien et al., 2005).

Following the fitting of the EEG the baseline recording with no active suppression began. Participants were asked to sit in a semi-reclined position and with their eyes open. The participants were also informed that they were free to tic during this recording if they needed to. The recording was taken in one session, three minutes in
length. The data in this recording session was later used to calculate the resting coherence for eyes open. The first recording was then followed by a one-minute break.

After the baseline recording was completed, and following the one-minute break, the active suppression recording was administered. Once again, the participants were asked to sit in a semi-reclined position with their eyes open. Unlike in the first recording, the participants were asked to actively suppress their tics during the recording. Just as in the first recording the participants were recorded in one three-minute session. The data from these recordings were later used to calculate the eyes open active suppression coherence levels.

Once another one-minute break was completed a second baseline reading was taken. In this recording participants were once again asked to sit in a semi-reclined position, however in this recording participants were asked to close their eyes. As earlier, the participants were informed they were free to tic during this recording if required. The recording was taken in one session, three minutes in length. The data in this recording session was later used to calculate the resting coherence for eyes closed.

Following another one-minute break, the eyes closed active suppression recording was administered. The patients sat in a semi-reclined position with their eyes closed. The participants were once again asked to actively suppress their tics during the recording intervals. Recordings were taken in one three-minute session. The data from these recordings were later used to calculate the eyes closed active suppression coherence levels.
2.2 **Data Analysis:**

The data from both sets of recordings were then transferred from the recording software (Scan 4.3; Advanced Medical Equipment) to Matlab for data processing. A 30 second window, that contained no signs of movement or tics, was visually chosen from the EEG recordings of each participant. The recordings were then filtered using a fourth order bandpass filter (.5-100 Hz). The filtered 30 seconds from the EEG recordings were then used to find the coherence between F3-C3, F4-C4, FCz-C3, and FCz-C4, with specific attention paid to the alpha frequency band (8-12 Hz). The coherence was calculated using the equation $|R_{ab}(\lambda)|^2 = |f_{ab}(\lambda)|^2 / f_{aa}(\lambda)f_{bb}(\lambda)$. In this equation, the numerator indicates the cross spectral density between a and b and the denominator represents the auto spectral density for a and b respectively. The coherence values found through this process were then further analyzed using two methods. First, percentage coherence scores were calculated using the equation, $(P_a-P_r)/P_r x 100$ (Serrien et al., 2005). In this equation, $P_a$ represents the average active suppression data and $P_r$ refers to the average rest data for each individual. This calculation simply determines the percent change between the active suppression condition and the rest condition. The percent coherence changes for each of the five participants were then averaged to give an overall percent coherence change value. The data was also analyzed by using the averaged coherence values from all five participants. The averaged coherence values for each participant in the alpha frequency band, for both the active suppression and rest conditions, were summed. This summed data was then used to run a one tail T-test to
determine if there was statistical significance in the change of coherence found during active suppression.
3: RESULTS

The five subjects in this study were mostly males, with only one of the five being female. The average PUTs score was a 27 with the low being a 20 and the high a 34.

Figure 3A shows a mean centered graph of the percent change for the eyes open active suppression condition from rest. Overall this graph shows a percent increase in coherence for all five subjects of 5.8%, represented by the mean line. Four out of the five subjects had some increase in coherence from rest, with subject two through four all having an over 10% increase in coherence from rest. Subject five is the only individual that showed a decrease (17%) in coherence during active suppression.

![Mean Centered Percent Change in Coherence EO](image)

**Figure 3A.** Above is a mean centered percent change in coherence graph for eyes open. The mean line shows the average percent coherence change for all five subjects and the second line shows percent coherence change for each subject.
Figure 3B shows a mean centered percent coherence change graph for the eyes closed condition. This graph shows that in the eyes closed condition the coherence level increased on average by 21%. Subjects two through four all showed coherence increases of over 10%, with subject two showing a percent increase of 91%. Subject one and subject five both showed decreases in coherence, 4% and 8% respectively.

![Mean Centered Percent Change in Coherence EC](image)

**Figure 3B.** Above is a mean centered percent change in coherence graph for eyes closed. The mean line shows the average percent coherence change for all five subjects and the second line shows percent coherence change for each subject.
Both Figure 3A and 3B show overall increases in coherence among the five subjects. Figures 3C and 3D, however, both show that this overall percent increase was not statistically significant, $p > .05$. Figure 3C show the results of a one tail t-test for the eyes open condition. The increase seen in the overall coherence was not significant ($p = .38$) for this condition.

**Figure 3C.** Above shows a one tail T-test based off the sum of the coherence values in the alpha frequency band (8-12Hz) for both active suppression and rest in the eyes open condition.
Figure 3D shows the results of a one tail t-test for the eyes closed condition. Despite the overall percent coherence increase of 21% there is no statistical significance (p=.18).

Figure 3D. Above shows a one tail T-test based off the sum of the coherence in the alpha frequency band (8-12Hz) for both active suppression and rest in the eyes open condition.
4: DISCUSSION

Based on the results found there was no significant increase in coherence during active suppression of tics for either the eyes closed or eyes open conditions. This differs from the findings in Serrien et al.’s study (Serrien et al., 2005). There are a few differences worth noting from the original study that may explain the differences in results. In Serrien’s original study only two out of nine subjects showed any type of comorbidity (Serrien et al., 2005). And of those two subjects only one was shown to have OCD (Serrien et al., 2005). In contrast, out of the five subjects analyzed in this study three had been diagnosed with OCD. It has been shown in EEG analysis of patients with OCD there is a decrease in power in the alpha frequency (Karadag et al., 2003; Wong et al., 2015). The larger number of individuals with OCD in this study may have reduced the values of coherence in the alpha frequency, the exact frequency that Serrien showed coherence increases occur in individuals with mostly pure TS.

The potential confounding effect of OCD on the coherence increase found in the alpha frequency in individuals with TS needs to be further analyzed. It is estimated that around 50% of TS patients also have OCD (Robertson, 2000). Is the coherence increase during active suppression found by Serrien, applicable to the entire TS population or is it just applicable to the half of the TS population that does not have OCD? In this particular study, subject number five showed a large decrease in coherence in both the eyes open and the eyes closed condition, 8% and 17% respectively. This subject also seemed to be
displaying discomfort due to the position of the EEG cap possibly from comorbid OCD. This may account for the decrease in percent coherence change seen in this subject.

The low sample size of this study may have played a part in the lack of significant change in coherence during active suppression. In Serrien’s original study, nine individuals with TS were used to determine the coherence levels (Serrien et al., 2005). In this study, however, only five subjects were used to determine coherence levels. This small sample size led to high variances for both the eyes closed and eyes opened conditions. A larger scale study would help resolve this problem.
In this study, there was no significant increase in coherence during active suppression as seen in Serrien et al.’s study. The findings in this study add an additional dimension to Serrien et al.’s study. The previous study focused predominantly on subjects with mostly pure TS, however, it is has been shown that 50% of TS patients have comorbid OCD (Robertson, 2000). To further the understanding of the effects of active suppression on coherence levels in alpha frequency it is important to study TS patients with comorbid OCD. Does the decrease in alpha power shown to occur individuals with OCD hold true in TS patients with comorbid OCD (Karadag et al., 2003; Wong et al., 2015). If it is found that the alpha power decrease does hold true for TS patients with comorbid OCD it could mean that increased coherence levels are only seen in pure TS patients.

On the other hand, if increased coherence in the alpha frequency is shown to be true for all TS patients, this would imply the difference is just due to the small sample size and that a large-scale study should be created to validate previous literature. Furthermore, a study should also be created to explore how changes in the coherence level effect the manifestations of tics in TS patients. Changing the coherence levels in TS patients could be used as a tool to help reduce the manifestation of tics and improve the quality of life for TS patients.
6: REFERENCES


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