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Identifying Treatment Response of Sertraline in a Teenager with Selective Mutism using Electrophysiological Neuroimaging

Case Report

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Abstract

Background: Selective Mutism is described as the inability to verbally express oneself in anxiety provoking social situations and may result in awkward social interactions in school-aged children. In this case-report we present the baseline electrophysiological neuroimaging results and after treatment with Sertraline for 6-weeks.
Methods: A 20-channel EEG event-related potential recording was acquired during an internal voice task at baseline prior to the initiation of 50mg of Sertraline and then repeated 6-weeks after treatment with Sertraline. EEG signals were processed for movement, eye-blink, and muscle artifacts and ERP signal averaging was completed. ERPs were analyzed using Standard Low Resolution Brain Electromagnetic Tomography (sLORETA).
Results: At baseline, Sertraline increased the neuronal activation in the middle temporal gyrus and the anterior cingulate gyrus from baseline in the patient following 6-weeks of treatment.
Conclusion: Our findings suggest that electrophysiological neuroimaging may provide a creative approach for personalizing medicine by providing insight to the pharmacodynamics of antidepressants.

Keywords: Treatment Response; Neuroimaging; EEG; sLORETA; Sertraline; Selective Mutism.

Introduction

Selective Mutism is characterized by the failure of the patient to speak in particularly anxiety provoking social situations [1]. The ability to speak is not loss, but suppressed in explicit circumstances. In these patients, stressful situations include the school environment, communicating with strangers, playmates, or distant relatives. However, the same patient is able to both effectively speak in the home environment with parents as well as siblings. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines SM based on the following.
exclusion criteria: the inability to speak should not be caused by the following:

1. An organic inability rooted in language ability (comprehension and comfort speaking the language).
2. Another communication disorder, such as stuttering.
3. Concurrent diagnosis of pervasive development disorder, schizophrenia, or other psychotic disorder [3].

Several studies have shown the successful treatment of SM with Selective Serotonin Reuptake Inhibitors (SSRI's) [2-4]. There are a few articles in the medical literature suggesting that SM may actually differ from social anxiety [5-7]. Thus, we sought to investigate the pharmacodynamic of sertraline, dosed at 50mg/day for 6-weeks, using electrophysiological neuroimaging in a functional internal-voice. Our goal was to localize the pre-Sertraline and post-Sertraline functional brain activity and quantify the difference using the sLORETA global field power. Based on the mechanism of action of sertraline, we hypothesize that sertraline would increase the Standard Low Resolution Brain Electromagnetic Tomography (sLORETA) global field power and improve functional brain activity during the speech task.

Case Presentation

A 14-year-old female was brought in by her parents to the Department of Psychiatry at the Medical University of Lublin with the complaint of their daughter's inability to speak in social situations

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outside of the house. After a careful patient history and physical examination, it was noted that the patient was able to solely communicate verbally with her mother and father in the home environment. Further, the patient's father stated that he suffered from the same condition at 14-years of age and later grew to become an outspoken activists on his university campus. The patient was admitted to the adolescent ward and both physical examination and vital signs were all within normal limits. Following evaluation, the 14-year-old adolescent female was diagnosed with Selective Mutism and Sertraline pharmacotherapy was considered the best next step in management of the patient.

After consideration and consulting with the Neurophysiology Laboratory, consent for the non-invasive recording procedure was obtained by the family. Both standard resting-state EEGs and a custom Event-Related Potential (ERP) task measuring the patient's Internal Voice was created and tested. The patient served as her own control and our aim was to identify if cortical activation in the speech association cortex would be improved from baseline to 6-weeks post-treatment with 50mg/day of Sertraline. We hypothesized due to the mechanism of action of Sertraline a global increase in the signal power would be seen at the six-week period.

Methods

Patient

A 14-year-old female was admitted to the Department of Psychiatry at the Medical University of Lublin. Following admission of a 14-year-old female to the Department of Psychiatry at the Medical University of Lublin. After obtaining informed consent, electrophysiological neuroimaging testing was recommended. At baseline, both the patient and her father were not taking any medications and did not consume coffee, tea, chocolate, or any substances known to interfere with the electroencephalography recording. The father's EEG signal was recorded first and then followed by the patient.

EEG Testing Protocol

Both study participants were comfortably seated in a semi-recumbent position in a sound and lighted attenuated, electrically shielded, room during the EEG recording. The resting-state EEGs were recorded over the course 5-minutes with eyes closed followed by 10-minutes of rest. Then 5-minutes of EEG Event-Related Potential (ERP) testing proceeded using a custom internal-voice task (in the native Polish language) that was triggered with a screen prompting the patient to see: "*What is your name?*" (*Jak masz na imie?*) as the frequent visual stimulus and "*Say Hi*" (*Powiedz Czesc*) as the rare visual stimulus in the testing paradigm. Time-locked EEG event markers matched the simultaneous output on the computer screen and was later used for calculating the event-related potential (ERP) using the ANT-Neuro EEMagine Software. The protocol was conducted at baseline and following 6-weeks of treatment of the 14-year-old patient with 50mg of Sertraline. The EEG recording of the patient's father was only warranted at baseline for an inheritance-based comparison and therefore no further recordings were deemed necessary.

EEG Data Acquisition and Processing

The EEG recording environment was a semi-sound proof dimly lighted room with a viewing glass for ensuring our patient's safety to where the EEG Technician and Physicians are able to view the testing status of the patients. Data acquisition proceeded with the Cognitrace EEMagine system (version 3.3.0.2, Advanced Neuro Technology Software BV, Enschede, Netherlands) that uses a total of 20 Ag/AgCl electrodes according to the standard international 10/20 system at the following scalp locations: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, Oz, O2. Electrodes were referenced to linked earlobes and impedances were kept below 5 k**Ω**. A band-pass filter was set to 0.5–70.0Hz and signals were acquired at 256 samples per second with a 50Hz notch filter.

Following the recording of the EEGs both automatic and manual EEG artifact removal of eye, blink, head-movement, and muscle-artefacts were conducted. The stimulus-locked internal voice task ERP signal averaging was analyzed using the EEMagine EEG software (version 3.3.0.2, Advanced Neuro Technology Software BV, Enschede, Netherlands) and subsequent ERP signals were exported for further analysis using Standard Low Resolution Brain Electromagnetic Tomography (sLORETA) [9-11].

Dose-Response Simulations

Sertraline dose-response simulations were conducted in the R programming language (version 3.2.2, The R Foundation for Statistical Computing, Vienna, Austria) using the Multiple Comparisons Procedure-Modeling package [12-14]. This modeling package has been validated by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use and is used during clinical trials and has been used in this report to illustrate the serotonin transporter (5-HTT) occupancy in the anterior cingulate and prefrontal cortex that has been demonstrated by Meyer and colleagues [15, 16].

Results

Due to the focus of wanting to differentiate from stimuli response versus processing concrete text displayed on the screen that is commonly reported as the P300 versus N700, respectively, the findings will report source localization of N700 findings [17]. The electrophysiological neuroimaging results identified peak brain activity in the Inferior Frontal Gyrus within the Frontal Lobe when prompting the patient to, "Say Hi." The sLORETA Global Field Power (GFP) was 15.2 at the Montreal Neurological Institute (MNI) coordinates of X=-50, Y=45, Z= -10 located at Brodmann area (BA) 47. Following the six weeks of Sertraline dosed at 50mg/day resulted in a decrease in the sLORETA GFP to 2.34 and relocated peak cortical oscillations to the Middle Temporal Gyrus within the Temporal Lobe at MNI coordinates of X= -65, Y= -20, Z= -10 and BA 21. The comparisons of the pre-treatment and post-Sertraline treatment findings are illustrated in Figure 1.

In contrast to the aforementioned decrease in GFP, prompting the patient with the question of "What is Your Name?" resulted in an increase of the sLORETA GFP from a pretreatment value 21.5 to a post-treatment GFP of 58.5 at N700. At baseline, the peak brain activity was localized to the Middle Occipital Gyrus at the MNI coordinates of X= -20, Y= -100, Z= 5 and BA 18 of the Occipital Lobe. Whereas, the post-Sertraline functional brain response was in the Medial Frontal Gyrus of the Frontal Lobe at

Figure 1. Pre-treatment (left) and post-treatment (right) ERP neuroimaging findings at N700 response to a command.

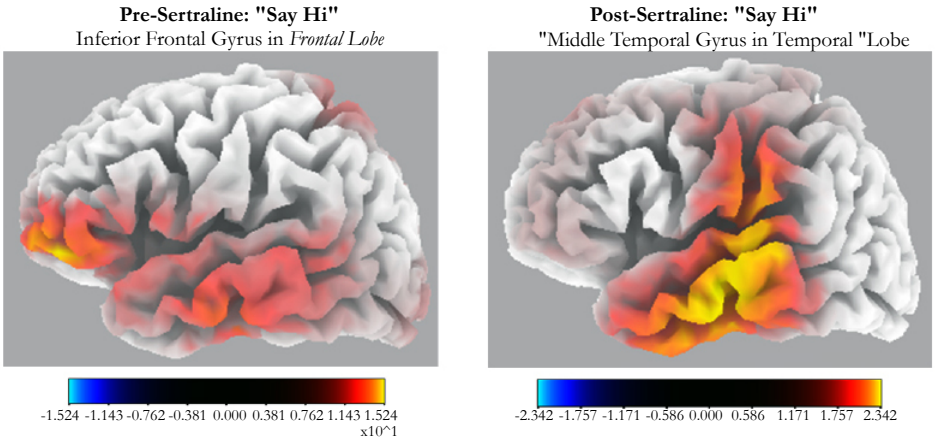


Figure 2. Pre-treatment (left) and post-treatment (right) ERP neuroimaging findings at N700 response to a question.

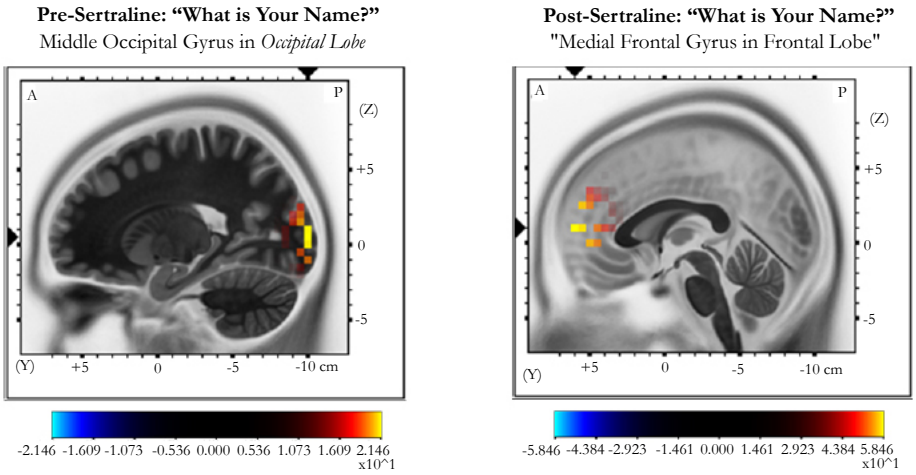
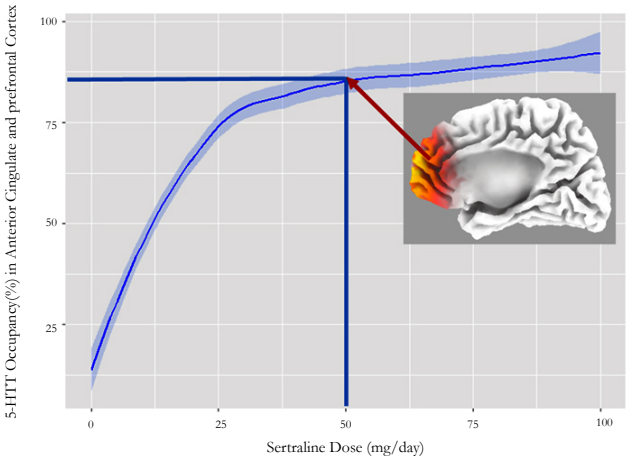


Figure 3. Dose-response simulations depicting the approximate serotonin receptor occupancy in the anterior cingulate gyrus and the prefrontal cortex as has been found in the clinical testing of 50mg/day for six-weeks.



MNI coordinates of X=0, Y=60, Z=10 and BA 10.

Further, to illustrate the dose-response relation of our findings relative to using a serotonin transporter occupancy model, dose-response simulations were conducted using the Emax model with an EC50 of 9.1 mg/day and an Emax of 100% as referenced from Meyer and colleagues [16]. The results illustrating the simulated population of 30 study participants at 21 doses totaling 630 samples are illustrated in Figure 3. Based on the simulations, our patient's daily dosing would have resulted in a 5-HTT occupancy of approximately 80%.

Discussion

Predicting treatment-response in pediatric psychiatry is of sincere concern for many parents prior to placing children on pharmacological intervention and maintaining adherence to medications. This case study shows that Sertraline, as Selective Serotonin Reuptake Inhibitor (SSRI), increased the neuronal activation in the middle temporal gyrus and the anterior cingulate gyrus from

baseline in an adolescent patient diagnosed with Selective Mutism. Functionally, our results suggest that the patient was capable of responding to a non-personal request of, saying hi using an internal-voice, however, when prompted a personal question of the patient's name, sertraline pharmacodynamics influenced the anterior cingulate gyrus.

These results may provide neurophysiological insight into the dichotomous thoughts of whether Selective Mutism is an anxiety disorder or a sub-classification of social phobia. Clearly, at both baseline and following treatment, the patient had the ability to speak; however, at baseline, there was significant frontal lobe and occipital lobe activation to saying hi and responding to her name, respectively. This may provide further insight to possible therapeutic interventions by using computer-based training programs to facilitate the vocalization of speech via neurofeedback.

Conclusion

Based on our findings, electrophysiological neuroimaging provides tremendous value when identifying treatment response to an SSRI in particularly vulnerable patient populations. Further, providing clear neurophysiological markers for the effects of antidepressant treatments may provide reassurance to parents of children, patients themselves, and insight to the clinical staff that would generally have to rely on non-biological markers of treatment efficacy.

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Conflicts of Interests: The authors declares no conflict of interests.

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