Biomarker Detection for Obsessive-Compulsive Disorder-related Distress

By

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Sc.B., Brown University, 2019

Thesis

Submitted in partial fulfillment of the requirements for the
Degree of Master of Science in Biomedical Engineering at Brown University

PROVIDENCE, RHODE ISLAND

MAY 2020

This thesis by Tanaya R. Puranik is accepted in its present form
by the Center of Biomedical Engineering as satisfying the
thesis requirement for the degree of Master of Science.

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Vita

Tanaya Puranik was born and raised in Cupertino, California. She attended Brown University for undergraduate studies where she studied biomedical engineering and was an undergraduate researcher in the Shukla Laboratory for Designer Biomaterials, an executive member of the Brown Biotechnology Investment Group, and a member of club tennis. During her undergraduate years, Tanaya worked on building next generation sequencing medical devices and catheter stabilization devices for infants in the NICU. During her master's program, she conducted research and data analysis as a part of the NIH Brain Initiative.

Preface

The work was conducted at Baylor College of Medicine (BCM) in collaboration with Dr. Wayne Goodman as a part of the NIH BRAIN Initiative. The team at BCM conducted the clinical recordings of the task and organized all data. Y-BOCS scores and medication information was recorded and scored by Greg Vogt, Carmen Vasquez, and Michelle Avendano-Ortega at BCM. The Conveyor Belt Task schema was designed by Nicole Provenza, Nicole McLaughlin, Eric Storch, and Evan Matteson, and associated hardware was built by Evan Matteson.

Acknowledgements

I would like to thank my advisor, Dr. David Borton, for his mentorship, guidance, and encouragement for this project. It has been a pleasure to be a part of his lab for the last year and I am immensely thankful for the privilege. I would like to thank Dr. Matthew Harrison for his guidance throughout the entire data analysis process and enthusiasm in mentoring me and my work. I would like to thank Dr. Nicole McLaughlin for her guidance, particularly in her neuropsychiatric and behavioral expertise for OCD. Next, I would like to thank Nicole Provenza, who generously brought me onto the project, offered endless advice to all my questions, patiently gave guidance, and was a pleasure to work with closely for the last year. I would like to thank Evan Dastin-van Rijn and the rest of the Borton lab for their support and collaboration and sharing the excitement of working on this project. Finally, I would like to thank my fellow students at Brown, my parents, my family, and my friends for their continuous support.

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ABSTRACT

Obsessive compulsive disorder (OCD) is a neurological psychiatric disorder that is characterized by impulses and intrusive thoughts, known as “obsessions”, and repetitive behavior known as “compulsions”. Neurological activity in OCD patients has been widely researched and several neuroanatomical models of OCD have been proposed. However, a physiological biomarker for the disorder has not been determined. In order to provide accurate treatment for closed-loop DBS and other treatment options, researching an accurate biomarker is vital for understanding which cortical loops and frequency bands to target for each patient. Literature presents conflicting and varying frequency band power increase and decrease, further proving the need for research into a biomarker for OCD. In this study, EEG signals were recorded during a Conveyor Belt Provocation Task that is designed to provoke an OCD participant continuously. This study proposes a continuous EEG analysis pipeline to investigate the effect of a continuous exposure stimulus that induces distress in the participant. This task was effective in provoking the participant as the object got closer and testing the effect of immediate exposure versus habituation to the object. Analysis of the EEG signals for biomarkers presented a variation between the participants, with three of the four participants having significant differences in EEG signal at a higher distress state defined by a higher self-rated distress during the task. One participant had an increase in the lower frequency band range, particularly theta and alpha bands in the prefrontal and supplementary motor cortex, and two other participants primarily had an increase in higher frequency bands in these lobes. An increase in beta and gamma was detected in the temporal lobe and somatosensory cortex as well. Overall, this study shows that the conveyor belt provocation task is effective in creating detectable changes in EEG signal from low distress to higher distress states for possible biomarker detection.

INTRODUCTION

Obsessive compulsive disorder (OCD) is a neurological psychiatric disorder that has a life-time prevalence of 2.3%.[1] OCD is broadly defined by unwanted thoughts and feelings (obsessions) and repetitive actions (compulsions). The obsessions can take form through thoughts, urges, or impulses, which causes distress and anxiety to the patient. To neutralize the thoughts and distress, the patient performs repetitive behaviors, which are compulsions.[2,3,4] Although healthy people may also release stress and perform compulsive behavior, these actions interrupt an OCD patient's day to day life.[3]

Symptoms of OCD

OCD can be triggered by a range of stimuli such as intrusive thoughts or a dirty object. For many people, the primary symptom of OCD is anxiety, discomfort, or distress.[3] OCD is usually linked to particular repetitive behaviors[9] and an inability to control these actions, and therefore is characterized by impaired self-regulation and lack of inhibition of errors.[5,6,7,8] Other behavioral symptoms include inflexibility in behaviors, [10] lack of inhibition to excessive responses[10,11], abnormal reward processings[12,13,14], and obsessive counting and ordering.[15] The symptoms of OCD are heterogeneous, and the range of behavioral symptoms are specific to the person.[3]

OCD severity is commonly measured using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).[16] Y-BOCS measures the severity and profile of the OCD over the past week or past two weeks. This scale is a clinician rated scale with 10 items that creates a subtotal for the severity of the obsessions and compulsions separately.[16] A strength of this assessment is that it can be used over time to monitor the patient's OCD profile. While this scale gives a

quantification of behavioral symptoms, it does not capture physiological changes in the brain while the patient is experiencing symptoms.[17]

Neuroanatomical models

To understand the physiological cause of OCD, neuroimaging techniques such as fMRI and PDG-PET, MRI, and CT are used identify regions of the brain that show varying activity in OCD patients from resting state and healthy controls.[18] Understanding which brain regions are associated with OCD is crucial in understanding the cause of OCD for each patient, for biomarker search, and for treatment options.

There are several regions of the brain that have shown higher or abnormal activity when provoked: the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), limbic/reward structures, thalamus, prefrontal cortex, amygdala, and basal ganglia.[18]

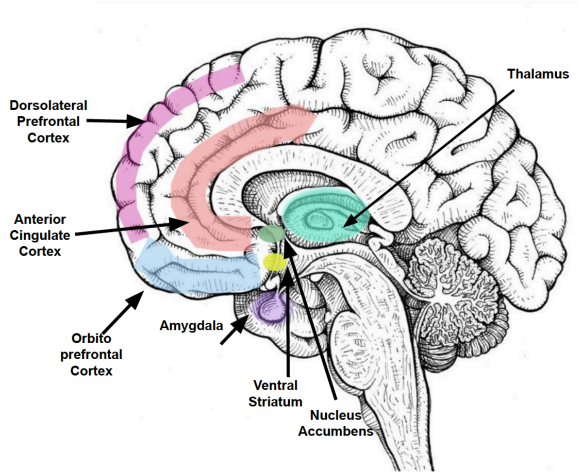


Figure 1. Brain Structures associated with OCD

The orbitofrontal cortex is associated with the integration of behavioral information, reward learning, and emotional processes.[19,20] The basal ganglia, specifically the ventral capsule/ventral striatum (VS) and the white matter fibers that connect the VS to medial prefrontal cortical regions, also are shown to be active in imaging studies.[21] Among imaging studies, OFC and basal ganglia are the two most commonly associated areas with OCD.[18] The anterior cingulate cortex (ACC) is associated with error detection and decision making and possibly with information processing,

negative emotional states, and anxiety.[18,25,26,27,28,11] A prominent OCD symptom is excessive error monitoring, which leads to repetitive compulsions and obsessions, and higher activity in ACC from PET and fMRI studies is reported in literature.[11,29,30] The prefrontal cortex has also shown activity in OCD imaging studies, and is associated with reward learning and complex behaviors.[11,18,30,31] Among this area is the dorsal lateral prefrontal cortex (DLPFC), which also has been identified as an active region during OCD symptoms.[11] The amygdala is associated with processing threatening, fearful, aversive, rewarding, and anxiety-inducing stimuli, and therefore is thought to be associated with information processing as well.[18,29] Limbic/reward structures are areas of the brain that are involved in the interaction of emotion, motivation, and memory and are broadly defined by the amygdala, hypothalamus, cingulate cortex, and hippocampus.[18] The final area of the brain associated with OCD is the thalamus, which shows higher activation in patients with OCD in comparison to healthy patients.[30,32] The thalamus acts as a "relay and integrative" site for other brain areas such as the OFC and basal ganglia, which are both activated in OCD.[33]

Understanding the physiological profile of OCD is important for future treatment to target the correct cortical loops that are causing the OCD symptoms. Several neuroanatomical models have been proposed for OCD. Previous models proposed ACC, OFC, and PFC to be the center of the model because of the association with error detection and reward-based decision making as well as the high activity in neuroimaging studies in these areas.[18] Currently, the "standard" model of OCD is the cortico-striatal-thalamo-cortical (CSTC) circuit, which combines the different areas of the brain that studies have shown to be active in OCD as seen in Figure 2.[23,33,34,35]

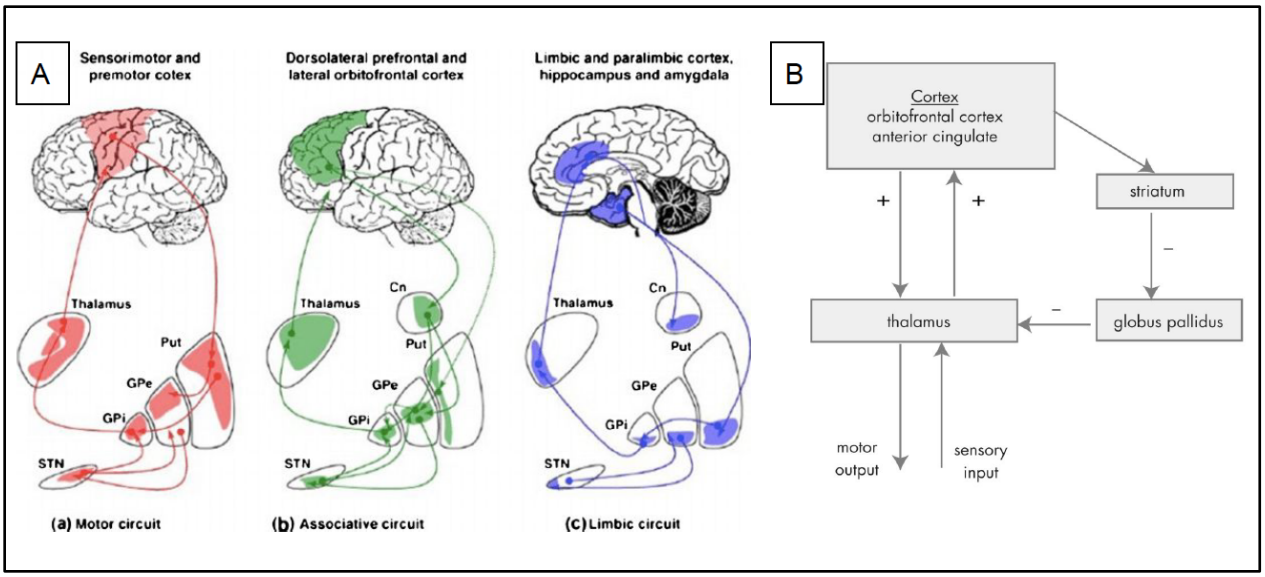


Figure 2. Cortico-striato-thalamo-cortical circuits for OCD. (A): Adapted from Lapidus et al. Example of three CSTC circuits targeted for OCD treatment[35](B) Adapted from Huey et al. Standard model of OCD[18]

Studies investigating the role of CSTC in OCD suggest that OFC, DLPFC, and paralimbic cortex are all different cortexes inolved in this loop.[35,36] Current studies are looking to see how these circuits work in parallel or together in patients with OCD.[18]

Another model proposed is the corticolimbic-VS information processing model, which involves the amygdala, OFC, and ventral striatum (Figure 3).[15] This model shows how impaired decision-making could lead to anxiety and exaggerated responses.

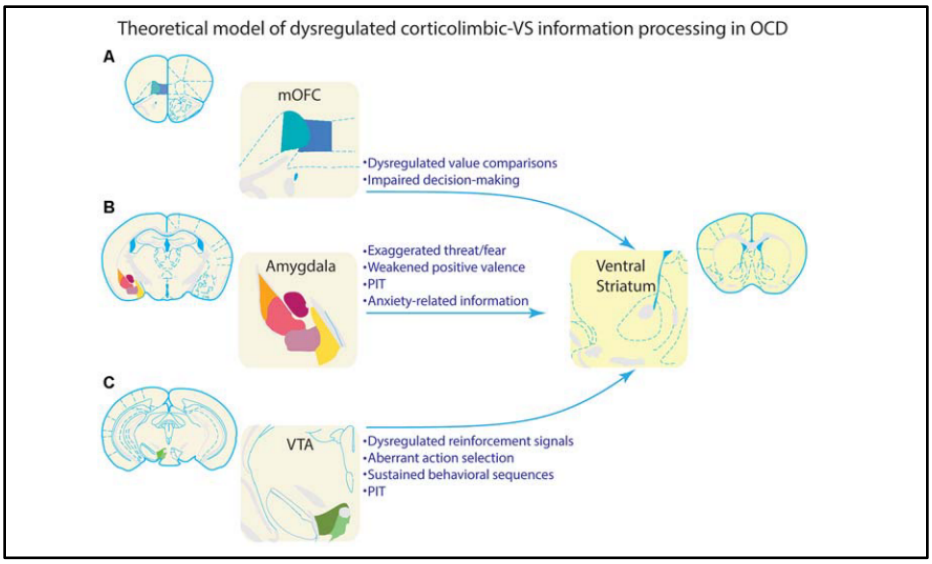


Figure 3. Corticolimbic VS information processing. Adapted from Wood et al.[15]

Features of EEG: Frequency Bands

Neuroimaging techniques are useful to identify regions of higher or abnormal activity for patients with OCD, and neuroanatomical models provide a basic framework for how these different regions interact.

One way to analyze brain signals and quantify the activity seen in the neuroimaging studies is looking at frequency band activity. Using methods such as electroencephalogram (EEG), the coordinated oscillatory activity of a group of neurons can be recorded. Not only is the location of the oscillatory EEG activity important, but these frequency bands have been linked to several neural processes. For OCD, delta activity (1-4 Hz) is considered to be associated with cognitive control and working memory.[3] Theta (4-8 Hz) activity is thought to be associated with information transfer in the hippocampus.[37] Alpha activity (8-15 Hz) is thought to be associated with task related activity. [38] Alpha is thought to increase when there is inhibitory control of task irrelevant processing and decrease in power when there

is less inhibition during a task.[38] Beta activity (15-30 Hz) and gamma activity (30 Hz-50 Hz) are associated with cognitive processing and thinking. [66,67]

Electroencephalogram (EEG) is an electrophysiological monitoring method that records brain signals through electrodes placed at the scalp and is a commonly used method to capture frequency changes in the cortex. For OCD, research has shown an increase in delta power during resting state in OCD patients compared to healthy control patients[3], a decrease of delta in DLPFC[41], and an increase in delta during the compulsive behavior.[39,40] Increased theta power has been recorded in the frontal temporal cortex[3,39] and in the ventral sub thalamic nucleus.[42] Decreased alpha power[2,39], increased beta power[3,43,44], and decreased beta power[39,43,33] have been recorded in various parts of the brain as well. Additionally, higher beta band complexity, a sign of more rapid fluctuation in EEG signal, has been found in the frontal lobe.[2,45] Literature commonly divides these broadly defined frequency bands into smaller regions labeled alpha1 (8-10 Hz) and alpha2 (10-13 Hz), for example, to examine any changes in a smaller frequency band range.[2,3] Differences and contrasting frequency recordings could be due to analysis in different regions of the brain, different methods of analysis, different choices of reference electrodes, and varying medications.[3]

Treatment for OCD and Need for Biomarkers

One treatment option for OCD is a pharmacological approach. Common treatment is clomipramine or selective serotonin reuptake inhibitors (SSRIs), which is effective in about 50% of patients.[46] In many cases, the treatment options do not work for the patient for reasons such as disease severity and profile, lack of treatment compliance, and constant

exposure to stress. Cognition behavioral therapy, specifically called Exposure and Response Prevention (ERP) for OCD, is also a treatment used for OCD, where the anxiety-inducing stimulus is exposed in hopes of normalizing that stimulus so that there is little response to that stimulus. [68] Another more invasive treatment option is Deep Brain Stimulation (DBS), which typically targets the ventral striatum/ventral capsule to directly stimulate areas of the brain to relieve symptoms, and has been found to improve OCD symptoms on average by 60%.[47]

A study looking at treatment effectiveness for OCD found that OCD patients that responded to pharmaceutical treatment had significantly lower beta activity (15 Hz-30 Hz) and lower activity in alpha2 (10.5-12 Hz) compared to OCD patients that did not responded to treatment.[48] Additionally, past literature shows how diverse symptoms and frequency band activity for OCD can be. Different OCD patients may exhibit a different grouping of physiological signals, and thus different biomarkers, which is important to consider for analysis as each patient's symptoms may vary. For DBS, future studies hope to use a closed-loop system that actively monitors the brain for activity. This active feedback titrates the response to symptoms as they occur, which is both more effective and reduces any side effects of stimulation. [17] In order for these treatments to work, understanding exactly which neurological circuits are affected in a patient is crucial. Therefore there is a need to research biomarkers of OCD.

In this study, we aimed to identify biomarkers for OCD through extended exposure and continuous stimulation of provoking objects specific to the person. By monitoring the

electroencephalogram (EEG), we hope to detect the exact time periods and neurological response during the patient's periods of distress.

METHODS

EEG Setup

The study consisted of five OCD patients and was performed at Baylor University. The participants ranged from ages twenty-nine to sixty-nine and were all Caucasian. Twenty tripolar surface electrodes (Fp1, Fp2, AFz, F7, F3, Fz, F4, F8, FT9, FC5, FC1, FC2, FC4, FC6, FT10, T7, C3, Cz, C4, T8, CPz) were attached in the frontal lobe and midbrain regions according to a custom montage. The EEG signals were captured using an OpenEphys system at 30kHz (https://open-ephys.org/, https://cremedical.com/about/). The ratings, position of conveyor belt, and time points were captured with two rotary encoders that were sampled at 30 kHz (www.adafruit.com/product/377).

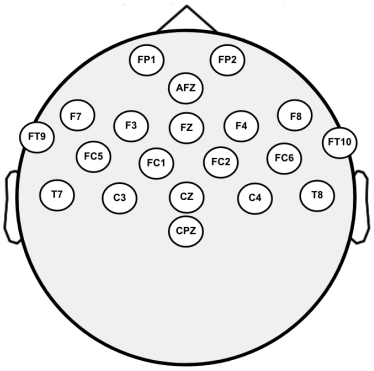


Figure 4: EEG setup: The EEG electrodes used in this study were primarily attached in the frontal and mid brain regions based on past literature of OCD stating higher activity in these areas.[23,33,34,35]

Conveyor Belt Provocation Task

The task used in this study is the Conveyor Belt Provocation Task that presents objects that cause distress to the person closer and farther from the participant.

Before the task, a psychologist picks three objects specific to the participant, two "provoking" and one "non-provoking". The provoking object is an object that induces distress or discomfort to the participant and the non-provoking object does not. For each of the three objects, the object was placed on a conveyor belt that moved closer and farther away from the participant each time as seen in Figure 6. The order of the objects were as follows: provoking, non-provoking, and provoking. Examples of provoking objects are a dirty t-shirt, rat food, and soap.

Figure 5. Conveyor Belt Provocation Task Setup. This is the setup of the Conveyor Belt Task at Baylor University as a part of the ABOVE study. The object in this image is placed at the farthest position from the participant. The readout board at the end shows the participant what they are rating when turning a rotary-encoder based dial.

To start the task for each object, the object was placed on the conveyor belt position the farthest away from the participant, defined as point 1. Then, the participant rated their distress on a scale of one to ten using a dial, and the readout of the dial was displayed on a monitor at the end of the table as seen in Figure 5. After this, the object moved closer and farther away from the participant in the steps as seen in Figure 6.

The conveyor belt sequence for each movement is as follows: The object moved for seven seconds to the next position, known as the conveyor belt movement period. Immediately after the object stopped moving, the participant had ten seconds to self-rate their level of distress on a scale of zero to ten. This period is defined as Rating Period 1. After this, there was a ten second waiting period where the conveyor belt does not move and the object stays at the same place, which is defined as the holding period. Then, the participant had

ten more seconds to self-rate their distress, which is defined as Rating Period 2. The holding period and second rating was added to see if prolonged exposure at the same position increased or decreased the participant's self-reported distress.

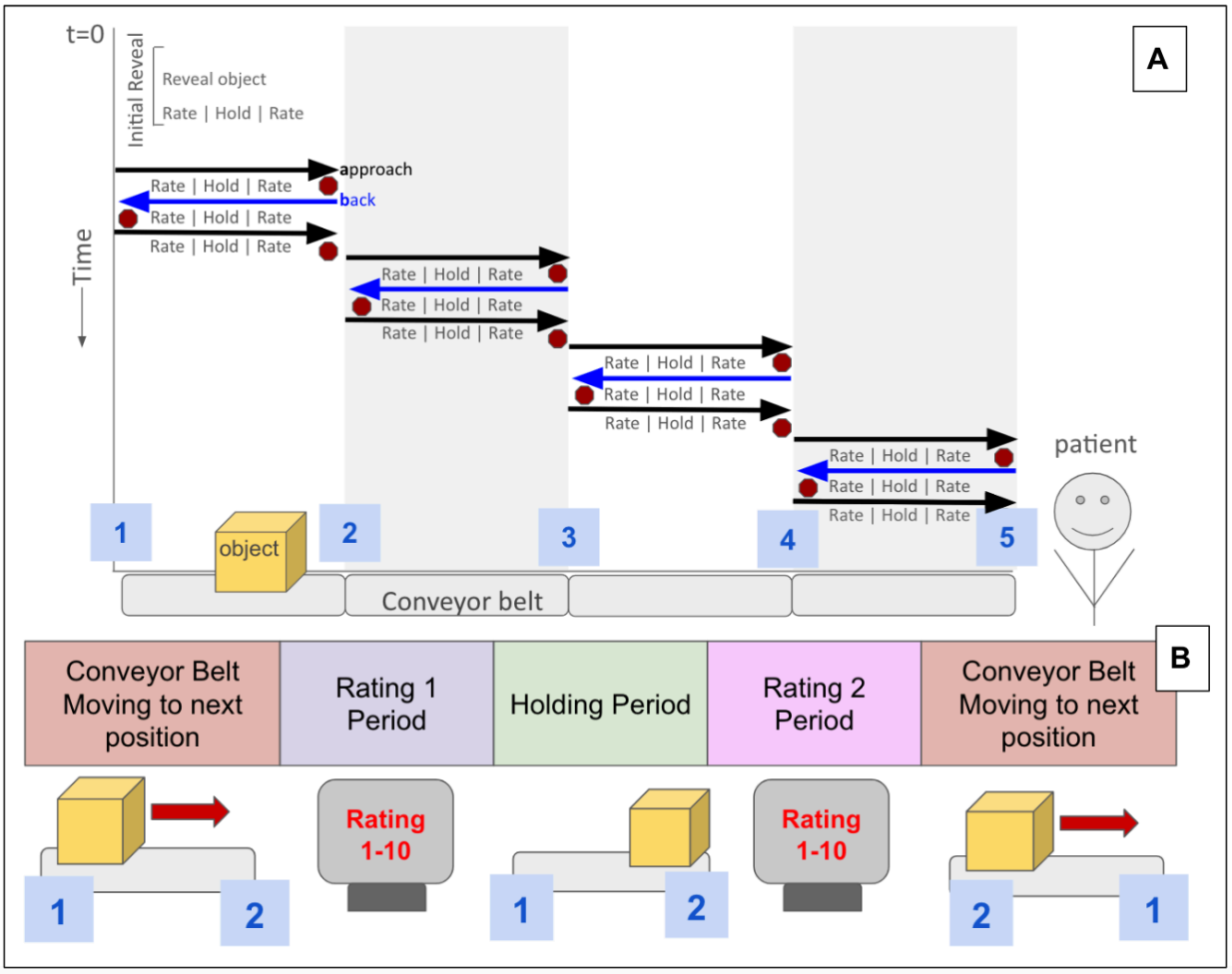


Figure 6. Diagram and timeline of Conveyor Belt Provocation Task. Part A: Adapted from Nicole Provenza. Depiction of Conveyor Belt Provocation task and the pathway of the object through the task. Position 5 is the position on the Conveyor Belt closest to the person and Location 1 is the position of the conveyor belt farthest away from the participant. Part B: The sequence of rating periods and conveyor belt movements.

There were 5 points on the conveyor belt where the object stops, with the 5th one being the closest to the participant. The object pathway is seen in Figure 6, where the object goes to the second stop, then back to the first stop, then to the second stop again, before going to the third stop and so forth. This means that the participant is exposed to the object at the same distance away two or three times during the duration of the task. The

entire task for all three objects and a brief break between the object takes about 25 minutes.

CONVEYOR BELT TASK ANALYSIS

The first step was analyzing the mechanical data from the conveyor belt provocation task. The conveyor belt movement was captured by one rotary encoder, and the rating amount was captured by another rotary encoder. Rotary encoders work by defining areas of "recording" and two pins that move either clockwise or counterclockwise when the dial is turned. When the pins pass the "recording area", a peak for both the pins is recorded. The number of peaks indicate the distance of movement on the conveyor belt, and the order of the different peaks indicate counterclockwise and clockwise movement, which in this case is increasing and decreasing ratings. The third data output of the rotary encoder is a peak when the rotary encoder is pushed down, which happens when the participant locks in their final rating. Figure 7 shows an example of the rotary encoder data for the rating dial and the ratings it correlates to.

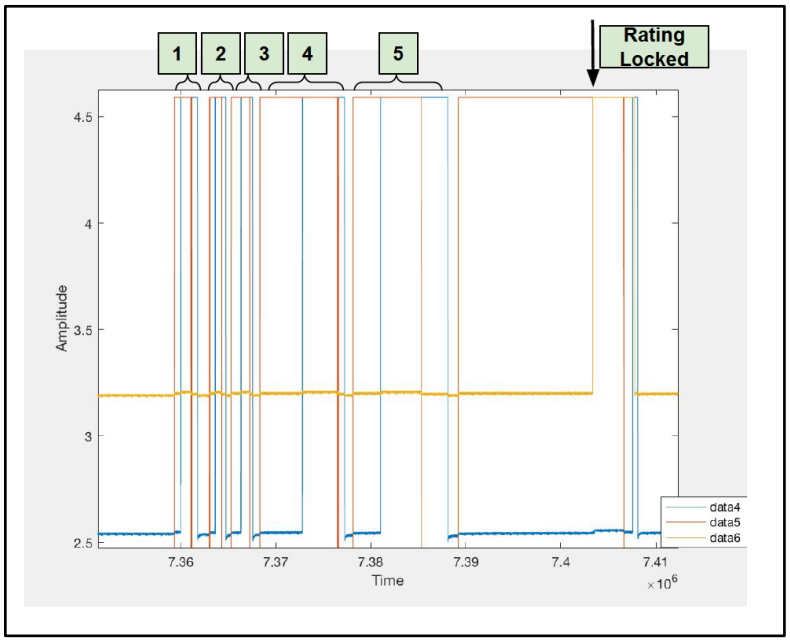


Figure 7:Rotary Encoder data. This is an example of the rotary data. When the red is in front of the blue, the ratings are increasing by peaks. As seen by the number of peaks and order of the peaks, the rating for the set is 5.

The output from the rotary encoder data are the position and timings of the conveyor belt, the ratings of the participant at each of the positions, and the start and end of the rating periods.

Outcomes of Task and Participant Behavior

The task was designed to have different periods of high and low distress and gives the participant a chance to rate their level of distress from zero to ten. The first step of analysis is to see how the participants reacted to the conveyor belt task by looking at the ratings at different points of the task and changes in the ratings based on conveyor belt position. The ratings, positions, and timings for each of the participant were analyzed and the following trends were identified. Analysis was done separately for each participant.

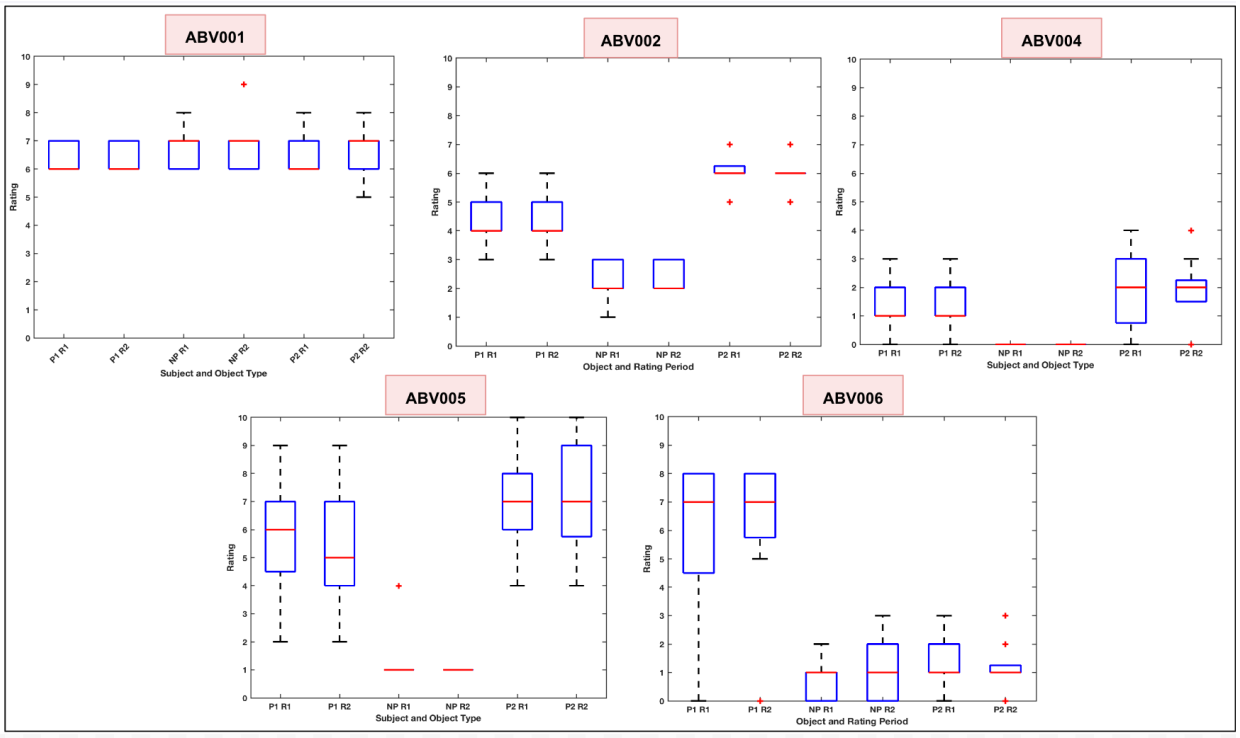


Figure 8. Rating distributions of the five participants. Position 1 is the farthest from the participant and Position 5 is the closest to the participant. This graph shows the distributions for rating 1 and rating 2 of the provoking objects and non-provoking objects. As seen, ABV001 does not have a difference in rating distribution between provoking and non-provoking objects and for ABV006, only one of the provoking objects was distress inducing to the participant.

1. Provoking objects were successful in inducing distress in participant compared to non-provoking objects

As seen by Figure 8, for participants ABV002, ABV004, and ABV005, the median rating and overall rating distribution for the provoking object was higher than the median rating and overall rating distribution for the non-provoking object, meaning that it was the distress-inducing object that provoked the participant's OCD symptoms. ABV001 did not have any difference in the rating distribution between provoking and non-provoking objects and this could be because the non-provoking object that was chosen did cause distress to the participant or overall having to do task was distress inducing to the participant. Additionally, participant ABV001 had the highest Y-BOCS score of 30, which could be related to the overall higher ratings of the objects (Appendix Figure 1). Participant ABV004 had the lowest Y-BOCS score of 19, and the maximum rating that participant rated was 4, which also could be related to each other. For ABV006, only one of the provoking objects caused higher distress to the participants. Another thing to note is that even though there are two provoking objects, the two provoking objects were not necessarily rated the same by the participant. Additionally, some participants did not use the full zero to ten scale to rate such as participants ABV002 and ABV004, where the maximum rating was 7 and 4 out of ten respectively. This could mean that the objects did not distress them to their maximum capacity.

2. Rating 1 and Rating 2 are similar for each position on the conveyor belt

Rating period 2 was integrated into the task to see if the participant's distress levels increase, decrease, or stay the same after a short period of habituation to the object at the fixed distance from the participant. However, as seen by Figure 8, the rating trends

between Rating 1 and Rating 2 for each object were similar, showing that the period of normalization did not change the person's self-rated distress.

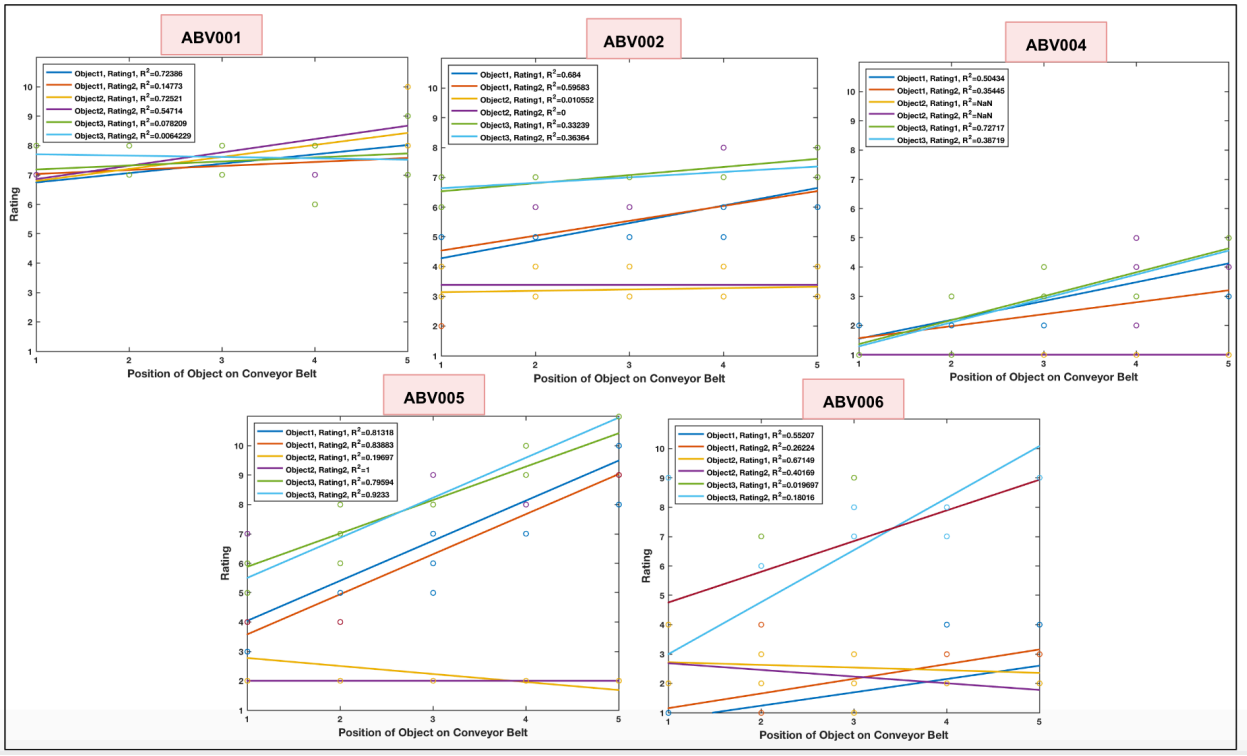


Figure 9. Ratings trends of each participant related to conveyor belt movement. Position 1 is the farthest from the participant and Position 5 is the closest to the participant. This graph shows the linear regression of the rating values to identify the relationship between ratings and the object position on the conveyor belt. This identification shows that all three objects provoked ABV001 and Rating 1 and Rating 2 were similar for all three objects for all of the participants. Five is the closest position to the participant and one is the farthest position from the participant.

3. Increase in ratings as object moves closer across all participants

Ratings increased as the object came closer to a person on the conveyor belt. This is significant for EEG signal analysis because this suggests that there is a positive relation between distance and self-rated distress for four out of the five participants as seen in Figure 9. Additionally, this shows that the distress increase was gradual and simply the presence of the object a distance away from the participant did not fully provoke the participant. The effectiveness of the non-provoking object in not causing high distress in

the participants even at the closest position gives a low distress state time frame for future EEG analysis.

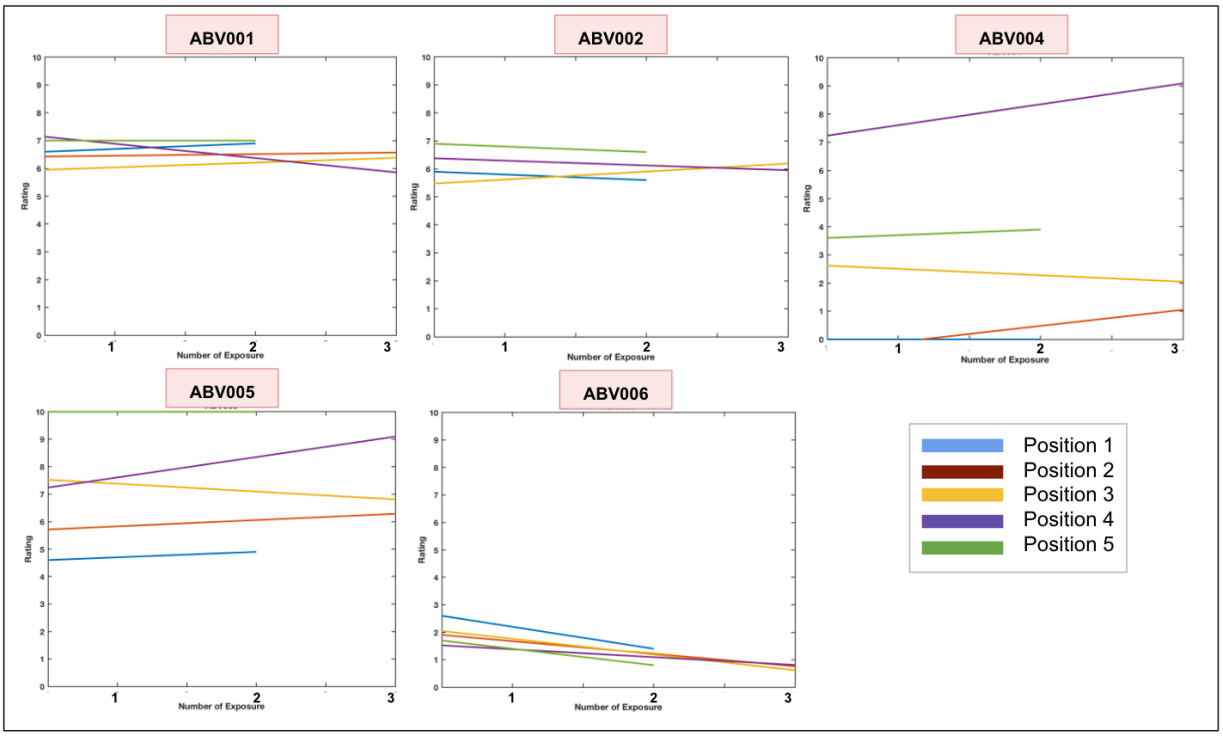


Figure 10. Changes in ratings depending on exposure number. This graph displays the linear regression of the rating values as the exposure number increases. With the exception of position 1 rating in ABV006 and position 4 in ABV004, all participants showed little rating difference as exposure number increased.

4. Exposure number effect on Ratings

During the task, the objects reached the 1st and 5th positions twice and reached the 2nd, 3rd, and 4th positions thrice. The metric used to capture this was labeled as 'number of exposures', which is defined as the first, second, or third time the object on the conveyor belt is at that certain position. As seen by Figure 9, this test was to see if the number of exposures increased, decreased, or consistently maintained self-rated distress. As seen with all five participants, overall there were no drastic increases or decreases in rating, with the maximum rating change at one position over time being 2. Depending on the participant, sometimes the number of exposures increased or decreased the rating slightly

as seen in Figure 9. Overall, the takeaway is that the ratings do not vary drastically over the exposure time for these five participants.

Key points for EEG analysis:

The first key takeaway is that there are moments during each task where the participant is distressed and less distressed, as seen through the ratings. This gives clear timepoints of a high distress and low distress states. The second takeaway is that there is not much of a difference between Rating 1 and Rating 2 for the five participants, meaning that habituation did not change the ratings and therefore self-rated distress was based on location of the object, not the amount of time the object was present. Similarly, the ratings did not vary much with exposure number. Third, the ratings increased as the objects got closer, so analyzing the object at a position closer and farther could be a metric of more distress versus less distress. Participant ABV001 was not used for EEG data analysis because the participant was continuously in a state of anxiousness and there was no resting state data to compare to.

Table 1: Participant information. This table captures the conveyor belt task rating range, Y-BOCS, and current medications for all of the participants.

Subject	Conveyor Belt Ratings	Y-BOCS total score	Medication	Age	Demographic information
ABV001	Minimum:6 Maximum:7	30	Prozac, 40 mg	34	Caucasian
ABV002	Minimum: 2 Maximum: 7	24	Fluvoxamine, 200 mg	59	Caucasian
ABV004	Minimum: 0 Maximum: 5	19	Fluvoxamine, 80 mg	29	Caucasian
ABV005	Minimum: 1 Maximum: 10	21	Lamotrigine, 200 mg Desvenlafaxine, 25 mg	34	Caucasian
ABV006	Minimum: 0 Maximum:10	26	Amlodipine, 10 mg Lisinopril, 40 mg Lipitor, 20 mg Mettorin, 500 mg Effexor, 75 mg	69	Caucasian

EEG SIGNAL PREPROCESSING

Filtering and Independent Component Analysis

First, the EEG signal was preprocessed using Matlab tools and the Fieldtrip toolbox on Matlab.[51]

Downsampling and Filtering

The EEG signal from the twenty channels was downsampled from 30 kHz to 1 kHz. A lowpass FIR filter for 50Hz and highpass FIR filter of 0.5 Hz were applied to filter out any noise such as the 60Hz electrical noise (although all wall outlets were unplugged during the task).

ICA and blink removal

Next, independent component analysis (ICA) was used to remove artifacts such as blinking. ICA is a computational method that works by dividing the EEG mixed signal into twenty independent non-gaussian signals, where similar frequencies and signal patterns are grouped together.[63] A few of these components are blinking as seen in Figure 11, which are then rejected using Fieldtrip functions.[51] ICA analysis ensures that minimum EEG signal is lost while removing artifacts by isolating the frequency and amplitude characteristics of the different signals. The effectiveness of ICA is seen in Figure 11.

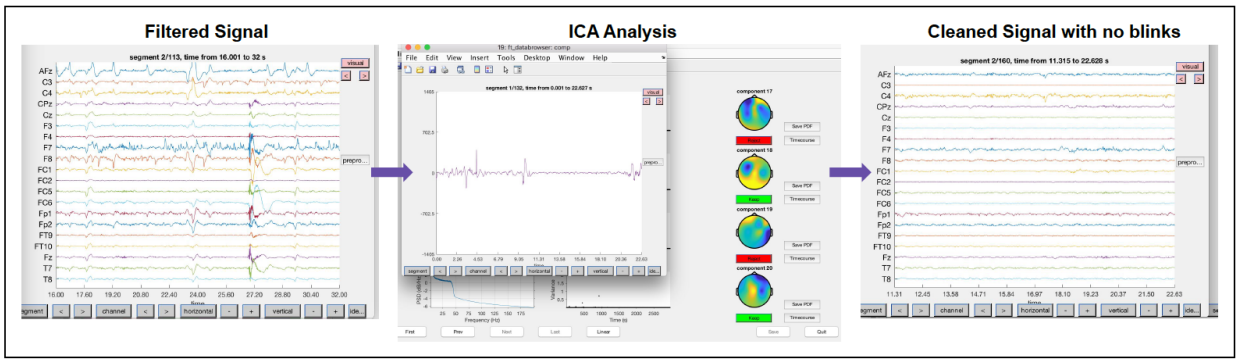


Figure 11. Effectiveness of ICA for removing artifacts. This process shows the difference between the filtered signal and the unfiltered signal and artifact removal using ICA. In the middle is the ICA window, where one of the twenty components is displayed. The blink is identified by the shape of the artifact, the larger amplitude than the rest of the EEG signal, and the location on the topoplot near the eyes. By rejecting this component, the similar looking peak is removed in all twenty channels.

Additional Artifact Analysis with Timepoint verification

ICA is effective in removing blinking, but in one participant there was still an artifact that crossed between the channels. To visualize the data, time periods from the conveyor belt task were overlapped on the EEG data, and the artifact was identified from video of the task as movement when the participant moved their hand to rate their distress. Sampling for future analysis for ABV002 was done around the movement period. At this point, any noisy channels were rejected as well. A noisy channel is due to either electrode malfunction or a poor setup of the electrode that led to high impedance. For subject ABV002, channel C4

looked noisy as seen in the EEG signal and topoplots. This means that during the setup, a strong connection was not created between the scalp and the electrode. Therefore for ABV002, any significant differences of frequency band in channel C4 cannot be confirmed.

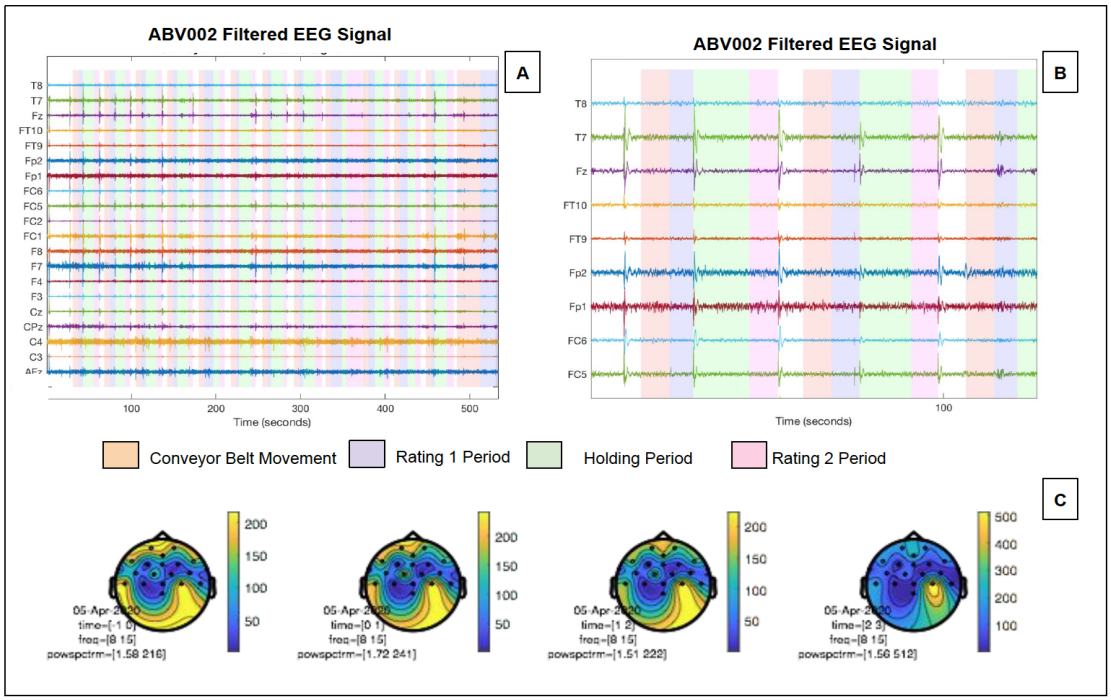


Figure 12. Visualization of EEG signal and time periods. *(*A) EEG data with timepoints (B) motor artifact detection in ABV002 (C) topoplot visualization for Noisy Channel: As seen by the intense yellow in the right bottom, the channel was noisy.

EEG ANALYSIS

Part A EEG Analysis: Evaluating epoched power spectral density

This task is unique in that the provoking stimuli, the object, is present for 8 minutes during the task. Other EEG tasks often have short stimuli such as a blinking image that produces a short response from the participant. The first method of EEG analysis done was looking at particular timepoints of a task and see if there a difference in the power spectral density for each frequency band between the high and low distress conditions. The different time periods during the Conveyor Belt Task were treated as “events”. The events were defined

as: the start and end of the conveyor belt movement, the start and end of rating 1 period, the start and end of the holding period, the start and end of rating 2 period.

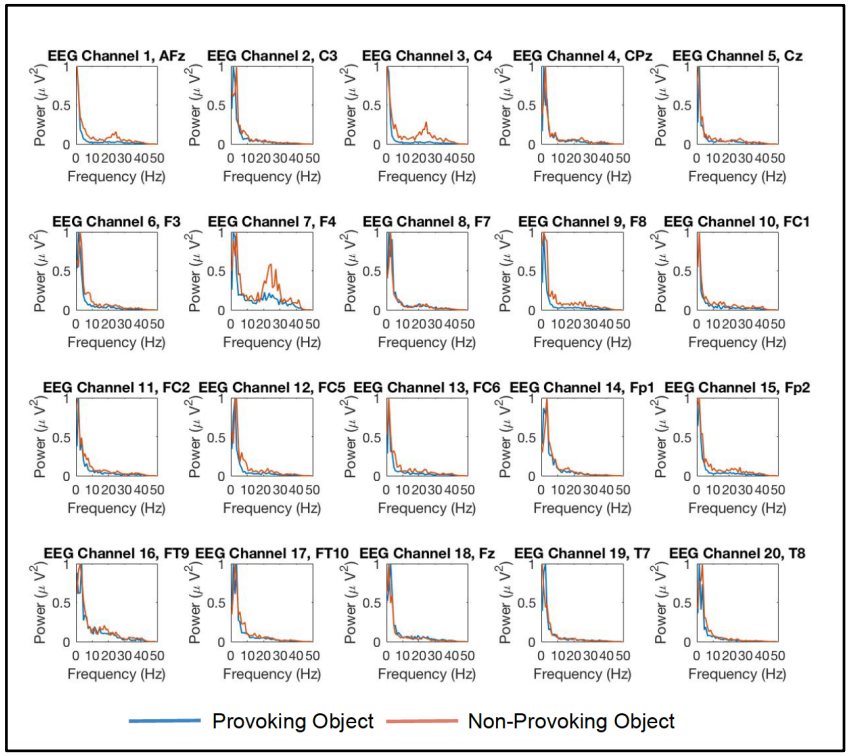


Figure 13. Epoched power spectral density. Analysis was performed using ft_frequencyanalysis function in the Fieldtrip Matlab package. In this example, frequency was averaged across all provoking object conveyor belt starting positions and all non-provoking conveyor belt starting positions.

Once these eight time points were identified, frequency analysis was performed on time scales of one second before to two seconds after, one second before to five seconds after the event, and one second before to ten seconds after the event using the ft_frequencyanalysis from the Fieldtrip toolbox. This method averages the power at each frequency band for the time range around the event. The frequency analysis was performed separately for all three objects, and both provoking objects were compared individually to the non-provoking object frequency spectrum as seen in Figure 13. A change between the provoking and non-provoking frequencies would indicate that at that specific time period, there was a change due to the provoking or non-provoking stimulus.

After analyzing frequency for four of the participants and all of the different possible event timepoints, only a few frequency differences between the provoking and nonprovoking objects were visible and no trends were identified between channels and frequency bands. During the course of the task, as seen with the conveyor belt analysis, the participant slowly rates higher and higher. Therefore, picking a single event as the triggering stimulus might not be effective in visualizing the gradual distress increase during the task. I opted to continue analysis of the entire EEG signal to see differences in the EEG signal between different timepoints of self-rated high distress and low distress instead of sampling only around a small period.

Part B: Continuous EEG signal analysis for feature extraction

To analyze the EEG signal for different frequency bands, the first step was to identify the power spectrum of different frequencies across the entire task.

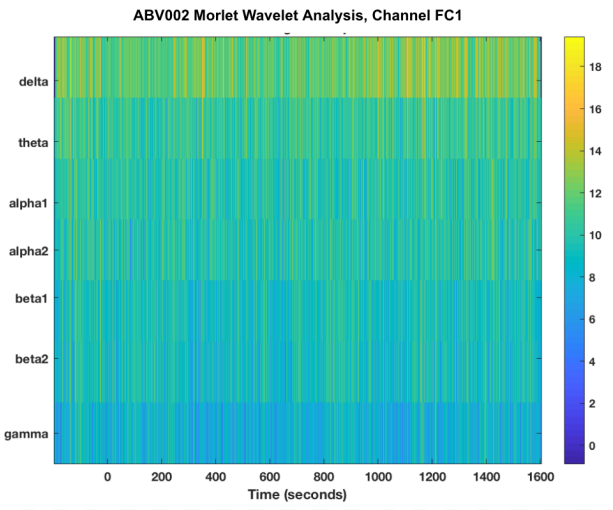


Figure 14. Morlet Wavelet EEG analysis. Analysis done using FIELDTRIP function ft_specest_wavelet.[51] Visual Representation of the morlet analysis on one channel for one subject. Frequency bands were combined as: Delta: 1-4 Hz,Theta: 4.0 Hz-8 Hz, Alpha1: 8 Hz-12 Hz, Alpha2: 12.5 Hz-15Hz, Alpha: 8-15 Hz, Beta1: 15-22 Hz, Beta2: 22-30 Hz, Beta:15-30 Hz, Gamma: 30-55 Hz. As seen in this figure, there are regions of high and low power for all nine frequency bands.

Morlet wavelet analysis

Morlet wavelet analysis is a commonly used method to identify the EEG frequencies and quantify the power spectrum of a single frequency band. A morlet wavelet is composed of a complex exponential carrier multiplied by a gaussian window and mimics

the EEG frequency signal.[53] This method essentially breaks down the mixed EEG signal for each channel into components by recognizing the frequency with the morlet wavelet pattern. This process was carried out on the downsampled and filtered EEG data using the ft_specest_wavelet function from the Fieldtrip toolbox in increments of 0.5Hz for the lower frequency bands (0.5Hz-15 Hz) and 1 Hz for the higher frequency bands (15 Hz and above).[51] The output of this function is an array of fourier coefficients, which when is squared and the logarithm is taken, which represents the power of the EEG signal at each frequency in units of $\frac{uV^2}{Hz}$. The output of this analysis is a power spectrum of each of the frequency bands for the entire task.

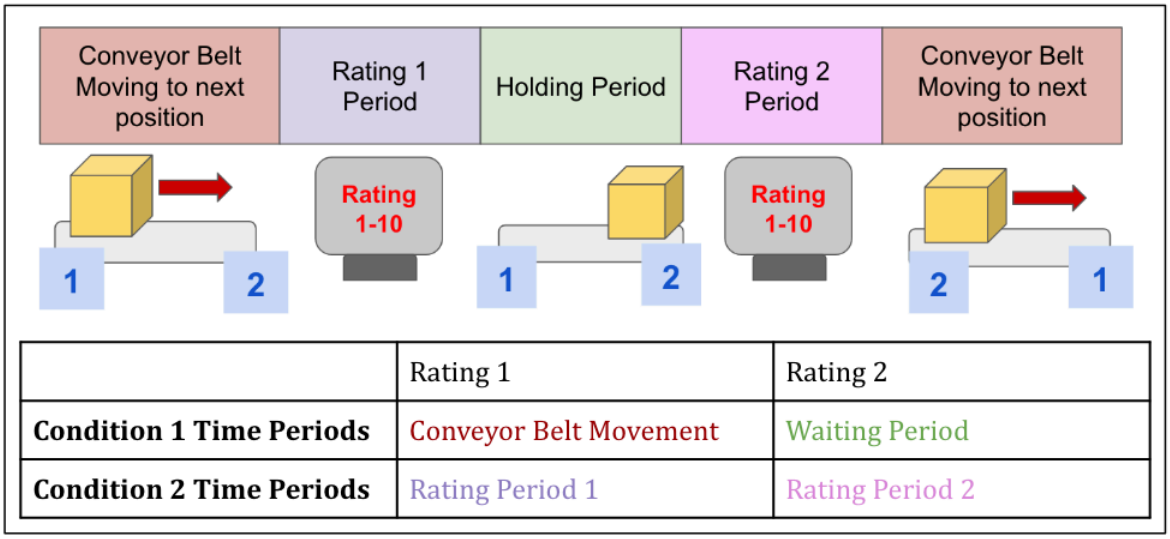
Next, the frequencies were grouped together into commonly defined neural frequency bands as follows: Delta: 1-4 Hz, Theta: 4.0 Hz-8 Hz, Alpha1: 8 Hz-12 Hz, Alpha2: 12 Hz-15Hz, Alpha: 8-15 Hz, Beta1: 15-22 Hz, Beta2: 22-30 Hz, Beta:15-30 Hz, Gamma: 30-55 Hz. Alpha and beta signals were broken up because they span multiple frequencies and multiple papers report that only specific frequencies in both the bands had detected changes during OCD and other neurological disorders.[3,39]

The first two goals were to characterize each time bin with a single statistical metric and find the exact time range for the individual participant where there was the most difference in EEG signal between high distress (high ratings) and low distress (low ratings).

Time periods for analysis

During the task, the participant rated their distress, and these time periods were used for

identifying the level of distress the participant was experiencing. There are four timepoints that this task could be divided into: conveyor belt movement, rating 1 period, holding period, and rating 2 period. The conveyor belt movement and rating 1 period are associated with the first rating after an object moves to a new position on the belt, and the holding period and rating 2 period are associated with with the distress after the object has been in a position for a while as demonstrated in Figure 15. During the conveyor belt movement and holding period, the participant is not moving and is watching the object. During the rating periods, the participant is reflecting on their distress and decision making. These four timebins were also separated into two separate time bins to analyze if changes in median EEG power were happening at a smaller time scale instead of the entire time bin. Confining the time bins for analysis is necessary to see the time scale at which changes in the EEG signal is happening and also prevent small bursts or changes in power from being washed out during statistical analysis.



	Rating 1	Rating 2
Condition 1 Time Periods	Conveyor Belt Movement	Waiting Period
Condition 2 Time Periods	Rating Period 1	Rating Period 2

Figure 15. Timepoints for continuous EEG analysis.

Identifying Trends in EEG Signal with Statistical Metric

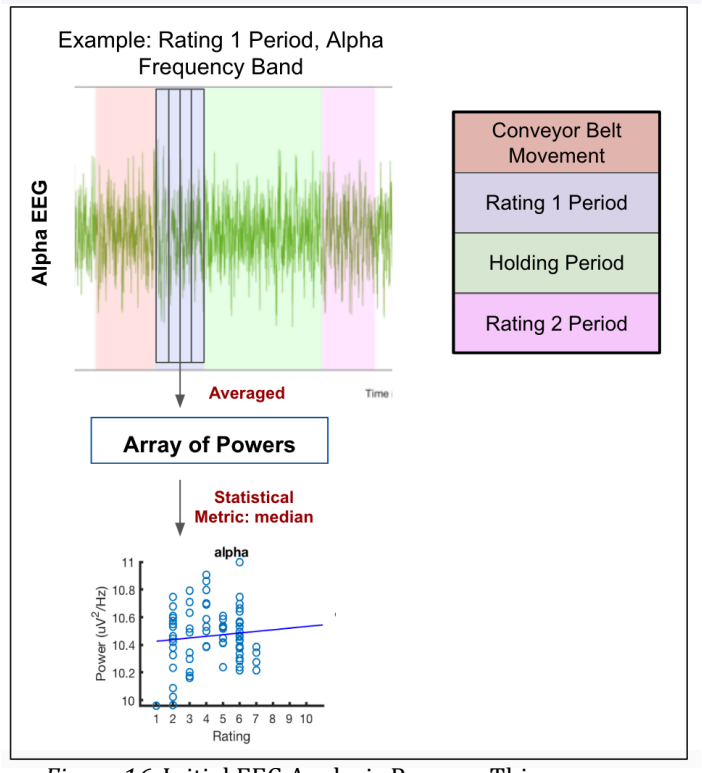


Figure 16. Initial EEG Analysis Process. This process was performed to detect any trends in the set and time points of maximum EEG signal change.

For each rating value, an array of power for all nine frequency bands was isolated for the conveyor belt movement, the rating 1 period, the holding period, and the rating 2 period. The power values were also isolated for these time conditions divided in half as well. To get these power values that are on a time scale from 0.001 seconds to a comparable number of cycles, the power of the frequency band was averaged into time periods of 1/(median of the frequency bands). For instance, for the theta band in the range of 4-8 Hz, the time band for averaging was ⅙ seconds, and for each second there would be six values of power. The averaging was also done on the scale of 1/(median of the frequency bands) instead of one or two seconds for all frequency bands so that any small changes in frequency at a short time scale, especially the higher frequency bands, were not lost when averaging the data. As seen in Figure 16, this produces an array of power for each rating value, frequency band, and channel.

Then, three different statistical metrics were performed on the power arrays for each rating: mean, median, and standard deviation. The statistic was visualized by plotting the

resulting statistic EEG power versus the rating value. The scatterplot was fitted with a linear regression model.

Scatterplots were made for each of the four participants, each channel, and each time condition. The criteria for visually identifying trends was a significant difference in EEG power between the lower and higher ratings with little overlap between the two values. The change in power between low and high distress states was quantified by the linear slope of the scatter plot as seen in Figure 16 and 17.

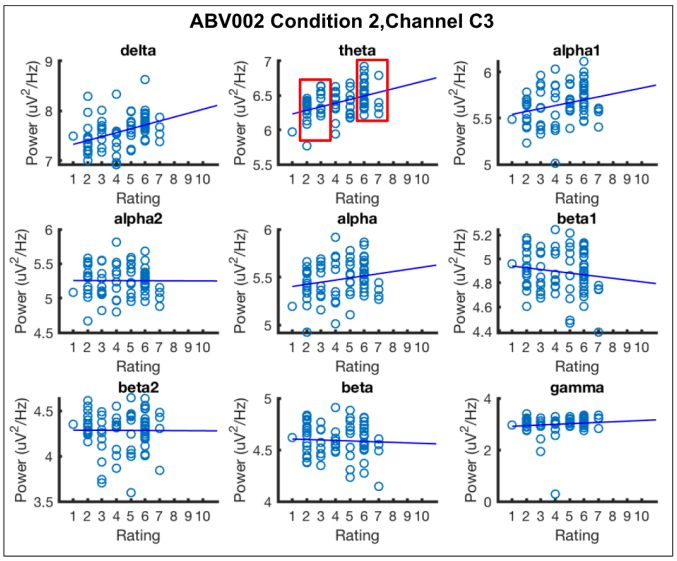


Figure 17. Median Scatter Plot. An example of a scatter plot with the median statistical test. In frequency bands delta, theta, and alpha 1, there is a clear visible trend between power and rating.

Although mean and median both had differences between the low and high distress states, the median was chosen as the statistic summary between these three statistics because it is less affected by outliers and there was the greatest difference in EEG power.

Approximate Entropy

Another initial statistical metric performed is defined as approximate entropy (ApEn. Past literature has applied this to EEG signal to measure rapid changes in EEG signal that could show bursting or increased fluctuations.[2] Entropy, also called complexity in EEG literature, measures rapid variations between consecutive and following datapoints. Literature has shown that a higher complexity in EEG signal, specifically a greater complexity in beta band, could be an indicator of OCD and epilepsy.[2,65,70] To calculate the ApEn, three input

parameters of time lag, tolerance of comparison (r), and length of input power are decided. The tolerance of comparison is equal to 1 to 1.5 times the standard deviation of the power array. Anything above or lower than this amount when comparing different points of the array is noted and increases the ApEn value. The ApEn values were calculated and plotted against the rating values to see if there were any trends as the ratings increased. As seen in Figure 18, an example of ApEn for Rating 1 and beta band of ABV005, there were no observable trends between the ratings and ApEn, even though there were fluctuations between rating to rating. This was true for the rest of the frequency bands, conditions, and subjects as well. Therefore, this was not used as a statistical test going forward, and the median was maintained as the best statistical metric.

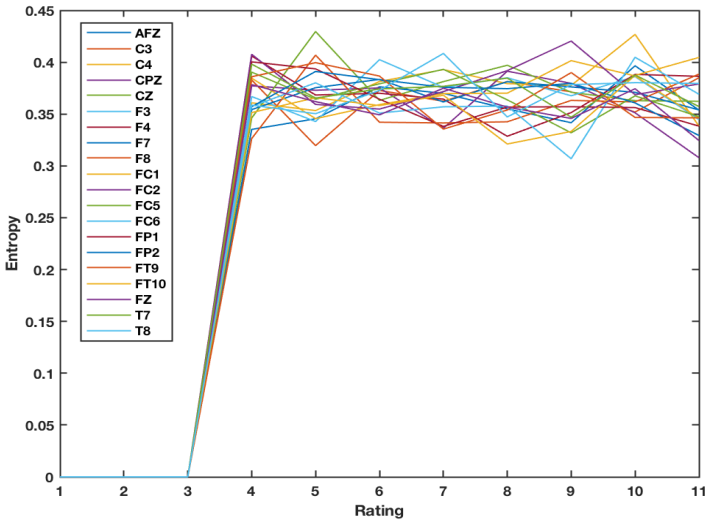


Figure 18. Example of Approximate Entropy Calculation (ApEn). As seen in the plot, there were no visible trends between low and high ratings and ApEn for each channel. A high ApEn means there are a lot of rapid changes in the EEG signal. In this participant, the lowest rating was 4, and thus the signal starts at rating 4.

Final Time Period Determination

Visual results from the scatter plots showed that dividing the four time periods into smaller time scales produced similar slopes as the slope for the overall time period it was a part of for the median statistic. However, there were differences in the slopes between the four different time periods, so the optimal time period for this task was the entirety of the conveyor belt movement, rating 1 period, holding period, and rating 2 period.

Behavioral Analysis

Based on the conveyor belt analysis, the scatter plots were analyzed to see if the power and rating trends were correlated with certain aspects of the task. The different behaviors tested were: rating 1 versus rating 2 ratings, non-provoking and provoking ratings, and close versus far ratings. During the task, participants did not rate different values for rating 2 compared to rating 1 for the same position, however, the task was designed to test whether a ten second habituation affects the response to the object. In all four participants, the provoking and non-provoking ratings as well as the close and far ratings were largely rated as low and high ratings, and therefore followed the same trends as the low to high ratings.

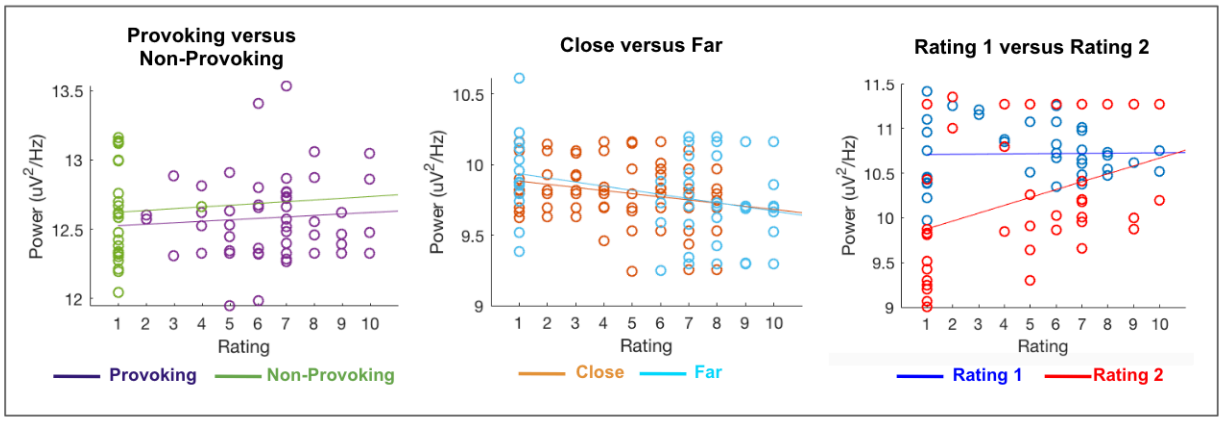


Figure 19. Behavioral Responses to Conveyor Belt. Examples of median EEG power grouping close versus far and provoking versus nonprovoking ratings were similar to low and high ratings. Rating 1 versus Rating 2 showed separation between the signals.

For three out of the four participants, for some frequency bands and channels, there was a difference in slope and median power between the two rating periods (Figure 18). This indicates that even though participants may rate the same signal, there could be a neurological change that was recorded though the EEG.

Next, all channels and frequency bands were examined in the scatter plots to see if the slope and distribution for rating 1 and 2 varied. As seen in Figure 20 and noted in Table 3, in participant ABV005 EEG, beta1, beta2, beta, and gamma slopes were different between Rating 1 and Rating 2 for all channels. In participant ABV006 EEG, beta1, beta2, and beta had a difference between Rating 1 and Rating 2 for all channels. In ABV004, the slopes varied for all frequency bands except for the gamma band for all channels and theta band in channels F4, F8, FC6, and FP1. Therefore, for analysis of these identified channels and frequency bands, rating 1 or rating 2 period were analyzed separately.

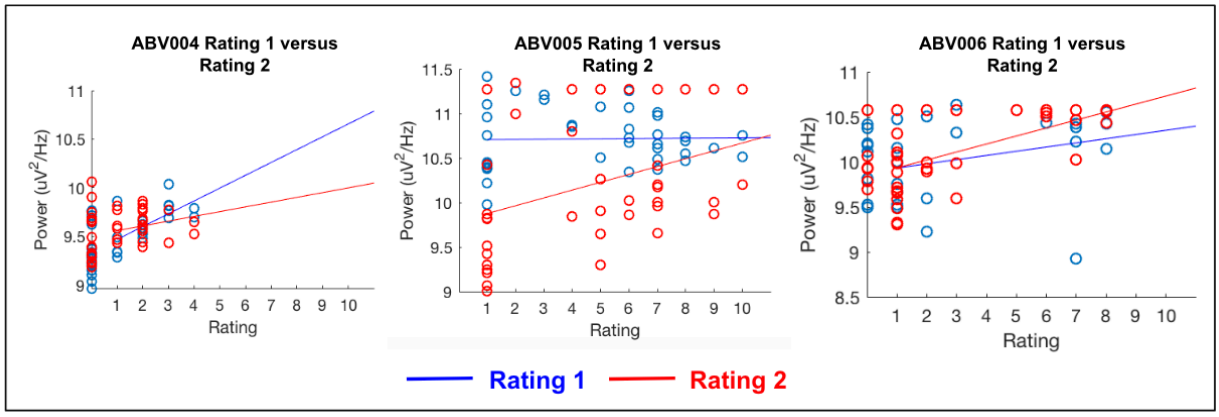


Figure 20. Differences in EEG power between Rating 1 and 2. Figure on the left is an example of a scatter plot of ABV005 EEG, and in beta1, beta2, beta, and gamma. Rating 2 has a positive linear correlation between EEG power and rating. In ABV006 EEG signal, Rating 2 only has a positive linear correlation between EEG power and rating in beta1, beta2, and beta.

Summary of results and decisions for analysis going forward

Statistical Metric

The statistical metric chosen as the best quantitative test for the EEG array is median and the number chosen to quantify the relationship between ratings and median EEG power was the linear slope as seen in Figure 16. The standard deviation and ApEn showed no clear difference between the higher and lower ratings. Although the mean had a similar

trend to the median, there were more trends with the median statistical metric and any outliers of particularly low or high powers would not heavily skew the outcome of the test.

Trends

The linear regression, specifically the slope from this regression, was used to quantify the difference in median EEG power between the low distress states and high distress states.

Table 2. Final Time Periods for Analysis

Test	**Time Period of Task**
Condition 1 All Ratings	Conveyor Belt Movement and Holding Period
Condition 1 Rating 1	Conveyor Belt Movement
Condition 1 Rating 2	Holding Period
Condition 2 All Ratings	Rating 1 and Rating 2 Period
Condition 2 Rating 1	Rating 1 Period
Condition 2 Rating 2	Rating 2 Period

Time Periods

This analysis for each participant showed that the time periods where there was a maximum difference in EEG signal from low to high distress periods was the conveyor belt movement, rating 1 period, holding period, and rating 2 period. The final data analysis was done with six tests for each subject using the median to capture the power array and labeled as follows: Condition 1 all ratings, Condition 1 Rating 1, Condition 1 Rating 2, Condition 2 all ratings, Condition 2 Rating 1, and Condition 2 Rating 2. To reiterate, condition 1 is when the object is moving or staying in place and condition 2 is during the rating periods when the participant has to self-evaluate their distress. Condition 1 all and Condition 2 all were used when there are no differences between Rating 1 and Rating 2 slopes.

Significance Testing

The total number of ratings across all three tasks is seventy-eight, with thirty nine ratings of rating 1 and rating 2 respectively. To test whether the slope increase or decrease is related to the OCD symptoms rather than chance, rating sample distribution, or noise, a permutation test with Bonferroni correction were performed.

First, for the permutation test, the median power values for each rating were randomly permuted, and the test statistic was the absolute value of the slope of the linear regression line from regressing median EEG power onto the ratings. For this study, 100,000 permutations were performed for every frequency band in each channel and participant. The p-value was calculated by the fraction of the test statistics greater than or equal to the observed slope (Figure 21).

The Bonferroni correction is a multiple-comparison correction that is used to correct for a false positive outcome that may occur by chance or unevenly distributed sample.[52] This test assumes that in the number of permutations performed, there is a probability of outcome by chance, known as the Family Wise Error Rate (FWER). The FWER is controlled using the Bonferroni correction by multiplying by the number or tests so that any low p-values that occurred by chance are reduced. The total number of tests performed with the dataset is 360, calculated from (20 channels* 2 time periods * 9 frequency bands). The adjusted p-value is the p-value multiplied by the Bonferroni correction factor. Any adjusted p-values lower than the alpha cutoff of 0.05 means that the null hypothesis is rejected, and that the increase or decrease in median EEG power as ratings increased or decreased could possibly due to the OCD-related distress and the probability of the results due to chance are lowered.

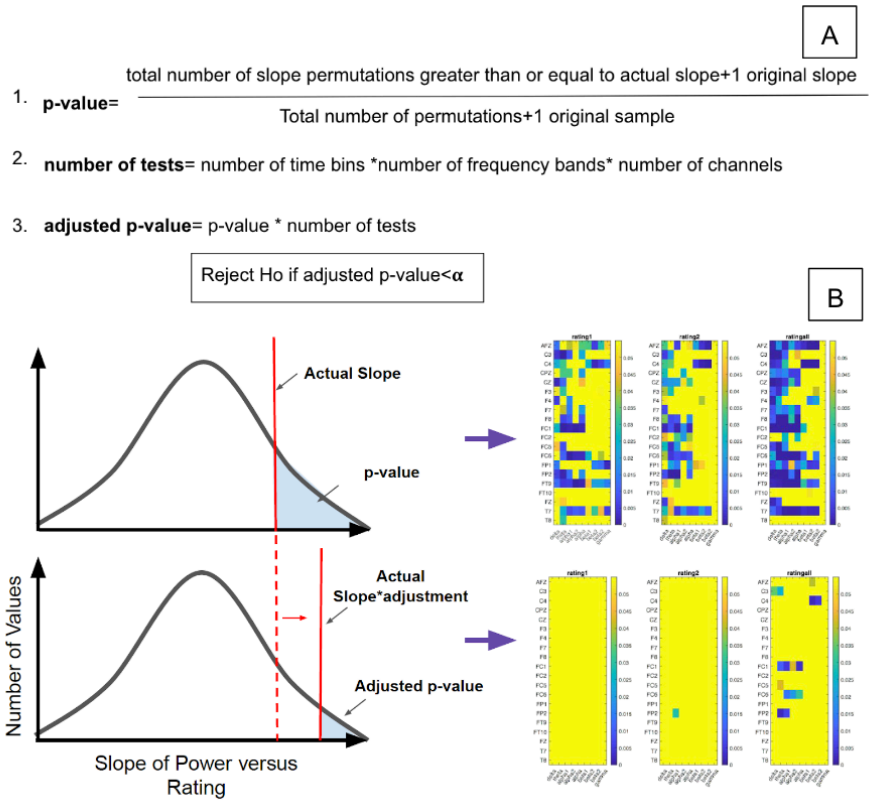
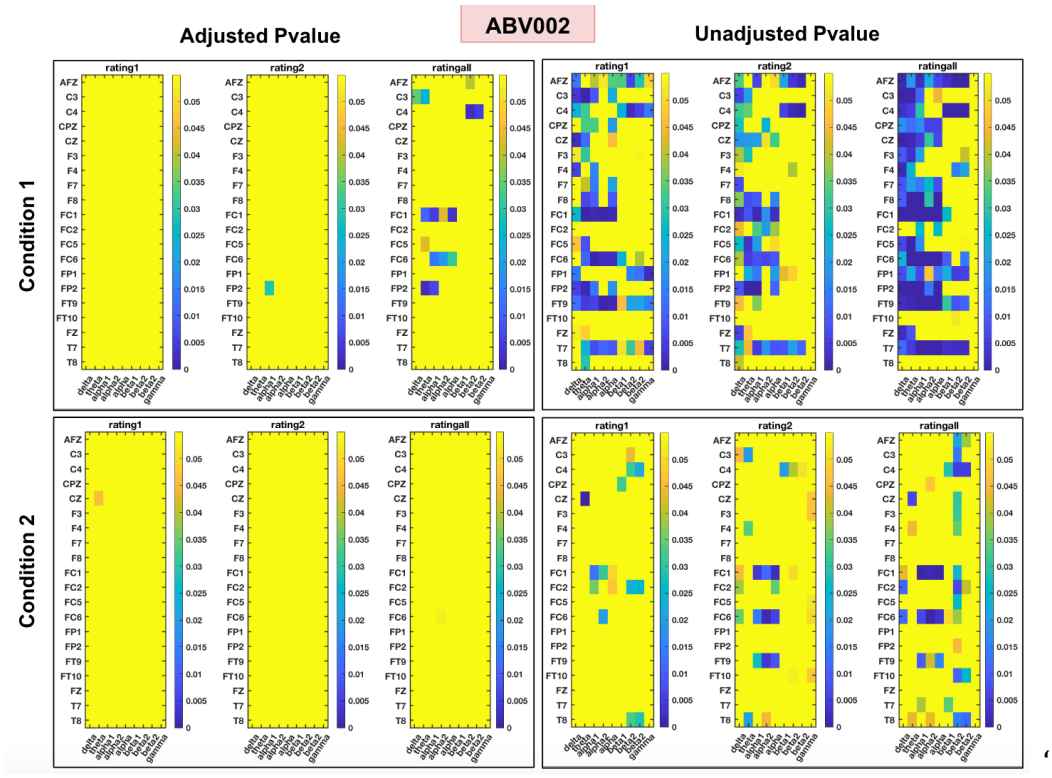
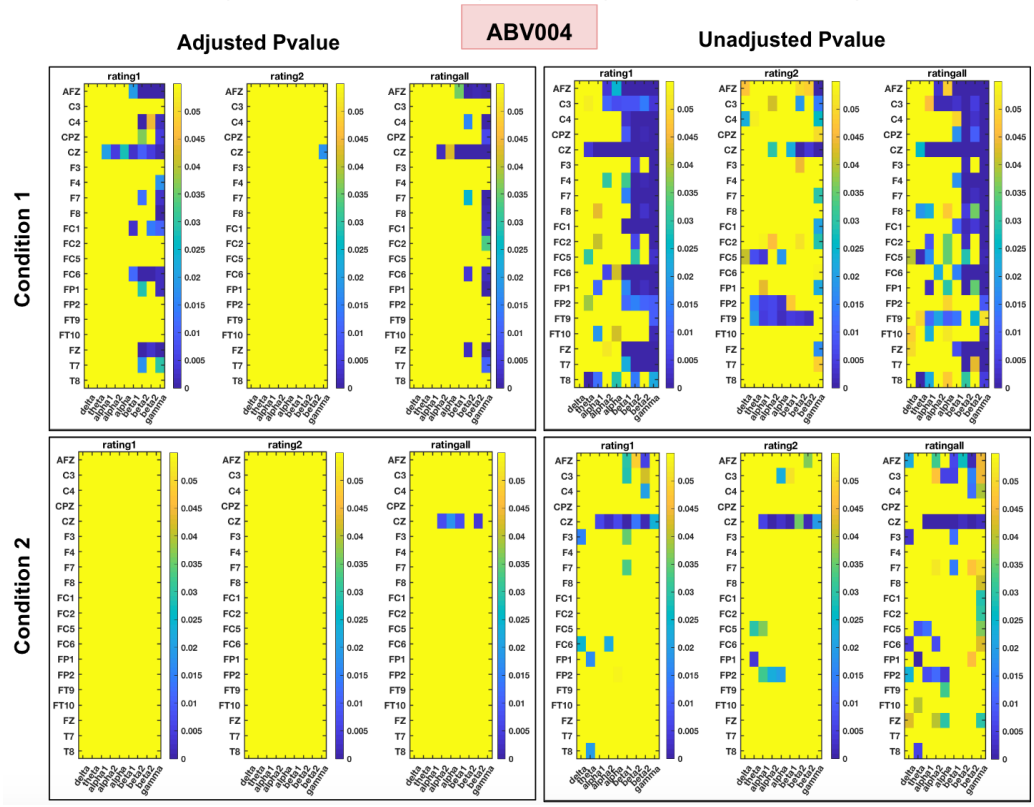


Figure 21. Bonferroni Correction Part A: Calculation for p-value and adjusted p-value. Part B: Visual interpretation of the unadjusted p-value and adjusted p-value. Any signal that is not yellow signifies that the adjusted p value was below 0.05, meaning that the change in EEG signal is possibly due to the OCD-related distress.

FEATURE IDENTIFICATION: FREQUENCY BAND CHANGES

As stated previously, adjusted p-values lower than 0.05 indicate that these channels and frequencies are possibly due to OCD symptoms and the participant being provoked. The next step is noting all channels and frequencies with significance. Figure 22 is a visual representation of the significant activity.


ABV002
Adjusted Pvalue
Unadjusted Pvalue
Condition 1
Condition 2
rating1
rating2
ratingall


ABV004
Adjusted Pvalue
Unadjusted Pvalue
Condition 1
Condition 2
rating1
rating2
ratingall

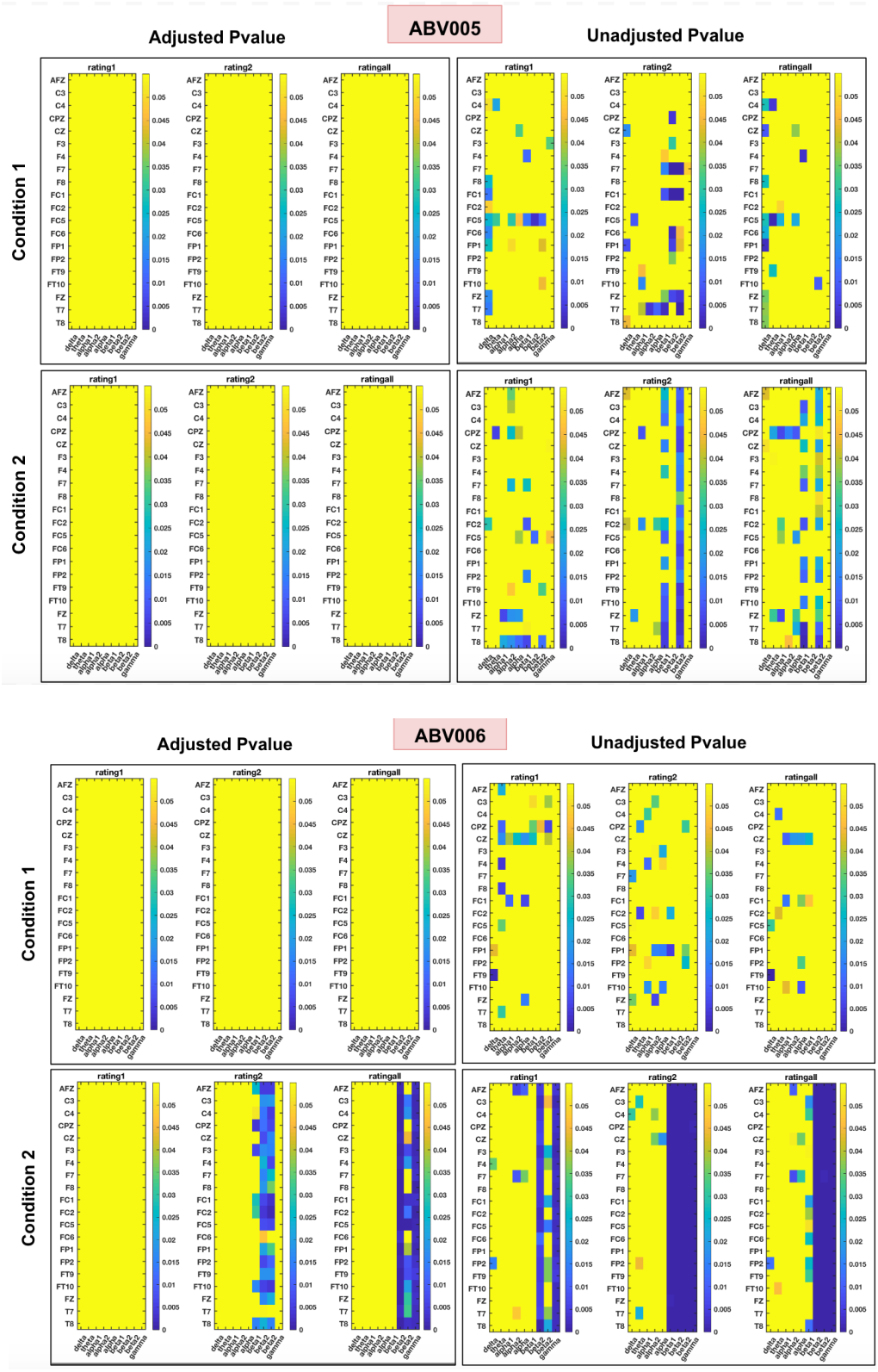


Figure 22. Adjusted p-values after Bonferroni correction. Adjusted p-values after multiplication with correction factor of 360. The unadjusted p-values are on the right and adjusted p-values are on the left. All boxes that are not yellow indicate that at these channels and frequency values the increase or decrease in EEG power could be related to OCD-related distress.

Table 3. Time Periods of EEG activity

Subject	Visual Difference between Rating 1 and Rating 2 Slope	Time Periods of EEG difference for further analysis	Other relevant Information
ABV002	None	Condition 1 all	Only participant with significant difference in lower frequency bands
ABV004	Yes: In condition 1, all frequencies except for gamma	Condition 1 all: gamma Condition 1 Rating 1: alpha1, alpha2, alpha, beta1, beta2, beta	Highest rating is five out of ten
ABV005	Yes: In condition 2, beta1, beta2, beta, and gamma	After Bonferroni correction, no significance	--
ABV006	Yes: In condition 2, beta1, beta2, and beta	Condition 2 Rating 2	All channels have at least one significant frequency band

From the adjusted p-value analysis, scatter plot visual confirmation, and spatial plotting of the frequency changes in each channel, time period, and frequency, any significant difference in EEG signal that could potentially be a biomarker of OCD was noted. As seen in Figure 22, there are no significant changes in ABV005 EEG signal after the p-value adjustment. Table 3 summarizes the timepoints used for further analysis and Figure 23 visually plots the significant activity in each electrode. Table 1 in the Appendix lists the full list of frequency bands and electrodes of significant activity.

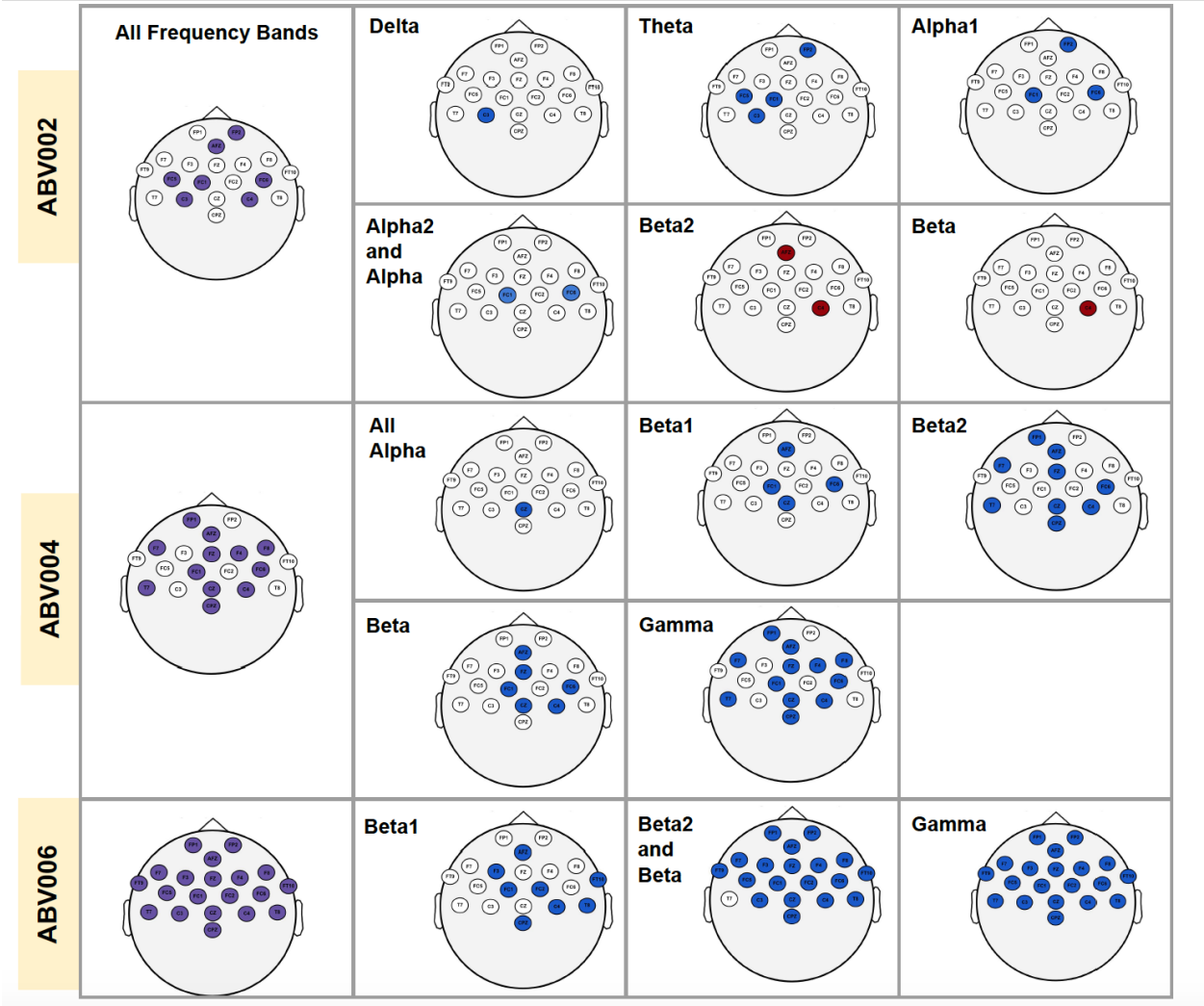


Figure 23. Spatial Representation of Frequency Bands. Blue represents a positive slope, meaning that the higher ratings had higher EEG signal, and the red represents a negative slope, meaning the higher ratings had a lower EEG signal than the lower ratings.

BIOMARKER ANALYSIS AND DISCUSSION

Neurological Relevance and Comparison to Past Literature

Each EEG electrode records from a specific place on the cortex. The next step is to correlate the frequency changes to the neuroanatomical area and compare the recorded signal to activity and EEG signals associated with OCD in literature. As seen in Figure 23, participants ABV002, ABV004, and ABV006 had significant EEG signal differences from low to high distress.

Table 4: Significant frequency change and associated neuroanatomy

Channel	**Area of Brain and Brodmann Area**	**Frequency**	**Participant Name**
OFC: FP1, FP2, F7, F8			
FP2	OFC (BA 10)	Delta and theta increase	ABV002
FP1 and F7	OFC(BA10 and BA47)	Beta2 and gamma increase	ABV004 and ABV006
F8	OFC(BA45)	Beta2 and beta increase	ABV006
Supplementary Motor Cortex and Premotor Cortex:FC1, FC2, FC5, FC6			
FC1	BA 6	theta increase	ABV002
FC6 and FC1	BA 6	Alpha1, alpha2, and alpha increase	ABV002
FC6 and FC1	BA 6	Beta2 and gamma increase	ABV004 and ABV006
FC6 and FC1	BA 6	Beta1 ,beta increase	ABV004
FC2	BA6	Beta1, beta2, beta, gamma increase	ABV006
Other activity			
AFZ	**BA9**	**Beta2 activity**	**Decrease: ABV002 Increase: ABV004, ABV006**
F3,F4	BA8	Increased beta1 and beta2	ABV006
F3,F4	BA8	Increased gamma	ABV004, ABV006
C4	BA 3 and BA 4	Beta2, beta, gamma increase	ABV004, ABV006
T7	BA 21 and 22	Beta2 and gamma increase	ABV004, ABV006
Overall activity		Beta2, beta, gamma increase	ABV004, ABV006

The EEG electrodes associated with the orbitofrontal cortex in this study are FP1, FP2, F7, and F8 electrodes. Two participants had significant increase in beta2 and beta activity in FP1 and F8 and gamma activity in F7 and F8 in higher distress states. Each participant had

at least one channel in the OFC with activity and two participants EEG had increased beta2 and gamma activity. This is consistent with literature including FDG-PET and MRI studies that have reported a range of left sided, right sided, or bilateral prefrontal cortex activity in OCD.[11,31,54,55,56,57] Studies done with lesions in Brodmann's area 10 and 11, which is FP1 and FP2, show that this causes dramatic changes in behavior leading to impulsivity, lack of judgement, loss of inhibition, and heightened emotions.[58] Compulsions and obsessions, as introduced in the background, are characterized by this lack of error monitoring and inhibition, and therefore higher activity in these channels in all three participants lends to these theories of the OFC role in OCD specifically with an increase in theta, alpha, beta2, and gamma signals.

Brodmann area 6 is the premotor cortex and supplementary motor cortex and is defined by electrodes FC1, FC2, FC5, FC6. This area is associated with planning complex, coordinated movements.[59] The medial part of Brodmann area 6 is the premotor cortex, which is associated with FC1 and FC2. In this area, all three participants had at least one significant increase in activity in FC1 and FC2, and at least one significant activity between FC5 and FC6. ABV002 EEG had an alpha1, alpha2, and alpha increase in FC1 and FC6, and ABV004 and ABV006 EEG had an increase of beta2 and gamma in the same channels. This result is consistent with literature that showed an increase activity in premotor and midfrontal cortex.[60]

T7 is located in Brodmann's area 21 which is the lateral temporal cortex.[57] The significant changes identified in this electrode are a beta2 and gamma increase in two of the three

participants. Literature reports increased activity in this area associated with a negative emotion response.[60,61]

Participants ABV004 and ABV006 EEG signal had a significant change in beta2 in electrode C4. This electrode is located in Brodmann area 3 and 4, which is the somatosensory cortex that borders the primary motor cortex. It is important to note that ABV002 EEG also had a change in beta2 signal, but C4 was a noisy channel in ABV002 EEG so the validity of this statement cannot be determined. The somatosensory cortex plays a role in emotional regulation, reevaluation of stimuli for emotional salience, and is thought to be connected to the amygdala and thalamic and limbic regions, which are a part one of the OCD neuroanatomical model.[62] Therefore this study shows that an increase of beta2 in this area could be a potential biomarker for OCD.

All three participants had a beta2 signal change in AFZ, which is located in Brodmann area 9, the medial prefrontal cortex and dorsal lateral prefrontal cortex (DLPFC).[11,57] Participant ABV002 had a decrease in beta2 signal and participants ABV004 and ABV006 had an increase in beta2 signal in this area from the low to high distress state. This area of the prefrontal cortex is associated with rule-learning, working memory, planning, attention, and motivation as well as being aware of sensory inputs, thoughts and actions, and changes in the surroundings.[56] Some studies have particularly pointed to the right DLPFC to be in charge of these functions, which is associated with electrodes F3 and F4.[11,57] Two participants had an increase in gamma signal and one participant had an increase in beta and beta2 signal in these electrodes. A lack of filtering of intrusive thoughts and heightened

sensory inputs are behavioral symptoms of OCD, and thus a change in beta2 in Brodmann area 9 could be a biomarker of OCD.

Summarizing Results

Overall, three participants had significant different EEG signals between low and high ratings during the conveyor belt provocation task, or low and high distress states. ABV002 EEG signal had a primarily lower frequency band increase (theta, alpha1, alpha2, alpha) and higher frequency decrease (beta2, beta) whereas ABV004 and ABV006 EEG signal had a higher frequency band increase (beta 1, beta2, beta, gamma). It is also interesting to note that ABV006 EEG signal had an overall high activity in all the channels in beta2 and gamma. Looking at the unadjusted p-values for ABV004 and ABV005, this trend is continues as well, indicating that there might be some relation between overall increased beta power and OCD symptoms.

The participants of this study reacted to the conveyor belt task in different ways; ABV002 had little slope differences between Rating 1 and Rating 2, ABV004 EEG signal had a large slope only in Rating 1, and ABV006 had a large slope only in Rating 2. These results show that physiologically there was little difference between initial and normalized exposure in participant ABV002, a physiological change after initial movement closer to the participant for participant ABV004, and a physiological change after continuous presence of the stimuli for participant ABV006. The median statistical summary was effective in quantifying an overall change in the EEG signal. It is important to note that not all median power values in

the high ratings were greater or different than the values in the lower ratings. This could be because the participant feels varying levels of stress throughout the task.

An interesting outcome of significant frequency activity is the overlap between certain channels but the differences in the frequency bands for each participant. This could vary because of medication and OCD profile, but also broadens the search for biomarkers and shows how personalized biomarker grouping could be for certain participants. Analyzing EEG signals from more participants for this task could show a few different types of frequency band groupings in certain areas.

KEY TAKEAWAYS

Identifying biomarkers of OCD will help in pharmacological treatment and for closed-loop DBS systems by targeting the correct area of the brain with abnormal activity. Through the conveyor belt provocation task, the physiological effect of a continuously present stimulus during OCD was recorded.

Participants of the task incrementally increased their ratings of distress as the object came closer, and in most cases, the ratings for the non-provoking object were a lot lower than rating for the provoking object, establishing a neutral and resting state for the participants. In four out of the five participants, the provoking objects chosen were effective in causing distress to the participant. Participants rated the provoking objects higher compared to the non-provoking object at the same position, showing that performing the task itself did not cause the participant distress, but only the stimulus of the object did. Although

participants self-rated a similar distress after initial movement of the object and after a ten second pause, the EEG signal varied between the two time periods in the higher frequency signals of beta1, beta2, and gamma in three out of the four EEG signals analyzed. Therefore for the same feeling of distress, a different neurological response may occur in initial provocation and continuous provocation. These differences show three different responses to a singular task, and how this can be used to neurologically and behaviorally understand a participant's OCD symptoms.

To analyze the results of this conveyor belt task and other longer, continuously present stimuli, this paper develops a pipeline for continuous EEG analysis. By using the ratings of self-reported distress, the task was divided into four major timepoints and divided into even smaller timepoints to isolate the primary location of maximum EEG change. Different statistical metrics such as mean, median, standard deviation, and approximate entropy were used to summarize trends and changes in the EEG data over various timepoints of no distress and distress. Once trends had been identified, the scatter plots were divided based on the different behavioral responses of the conveyor belt task to see if the signal varied due to a specific condition. Next, the permutation test with Bonferroni correction was picked as an appropriate significance test to ensure trends in the EEG data were not due to chance or dataset distribution errors. Then, all channels and frequencies for each participant where the rating 1 and rating 2 signals varied were noted and analyzed separately as well as a positive or negative increase in the frequency band from the lower to higher distress states.

Between the three participants with significant EEG data after the Bonferroni correction, all three had an increase in beta2 signal in channel AFZ, which is located on Brodmann area 9. All three participants had low or high frequency band increase in at least two electrodes in the premotor cortex and supplementary motor area. Two participants had an increase in beta2 and beta in electrode 'C4'. Overall, ABV004 and ABV006 showed a higher activity of beta1, beta2, beta, and gamma signal and ABV002 showed a higher activity of lower frequency signals of delta, theta, alpha1, alpha2, and alpha 3 in FC and prefrontal regions. All locations where significant signal was found has been associated with at least one OCD neuroimaging study and is involved with error monitoring, positive and negative emotions, decision making, and behavior repetition.

For future analysis, conducting more EEG studies with the conveyor belt provocation task would be useful to see if any groupings of biomarkers emerge at various timepoints of the task. This analysis would be helpful because, as detected in this paper, there was a low and high frequency response that varied between participants. Analyzing the effect of external factors such as medication, behavioral symptoms, treatment responsiveness, and stimulus type could also contribute to a complete understanding of biomarker detection. Characterizing all these responses would be helpful to build a predictive model and identify treatment approaches that can target certain loops as well as stimulate/inhibit the correct areas of the brain that are causing OCD for each participant.

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APPENDIX

Table 1. Biomarkers found in this study for each patient and frequency band. Frequencies highlighted in blue indicates a negative slope, or decrease in EEG power as the anxiety increased. Blue indicates a decrease in median power between low and high distress states.

	Condition 1			Condition 2		
	Rating 1	Rating 2	ALL	Rating 1	Rating 2	ALL
ABV002	--	Alpha1: FP2	Delta: C3 Theta: FC1, FC5, FP2, C3 Alpha1: FC1, FC6, FP2 Alpha2: FC1, FC6 Alpha: FC1, FC6 Beta2: AFZ, C4 Beta: C4	--	--	--
ABV004	Alpha1, alpha2, alpha: Cz Beta1: AFZ, CZ, FC1, FC6 Beta2: AFZ, C4, CPZ, CZ, F7, FC6, FP1, FZ, T7 Gamma: AFZ, C4, CPZ, CZ, F4, F7, F8, FC1, FC6, FP1, FZ, T7	Gamma: Cz	Alpha1, alpha2, alpha: Cz Beta1: AFZ, CZ Beta2: AFZ, C4, CZ, F7, FC6, FZ	--	--	Alpha2, alpha, beta1, beta: Cz
ABV005	--	--	--	--	--	--
ABV006	--	--	--	--	Beta1: AFZ, C4, CPZ, F3, FC1, FC2, FT10, T8 Beta2: all channels except T7 Beta: all channels Gamma: all channels	Beta2: all channels Beta: all channel except AFz, CPz, F7, F8, FC6 Gamma: all channels

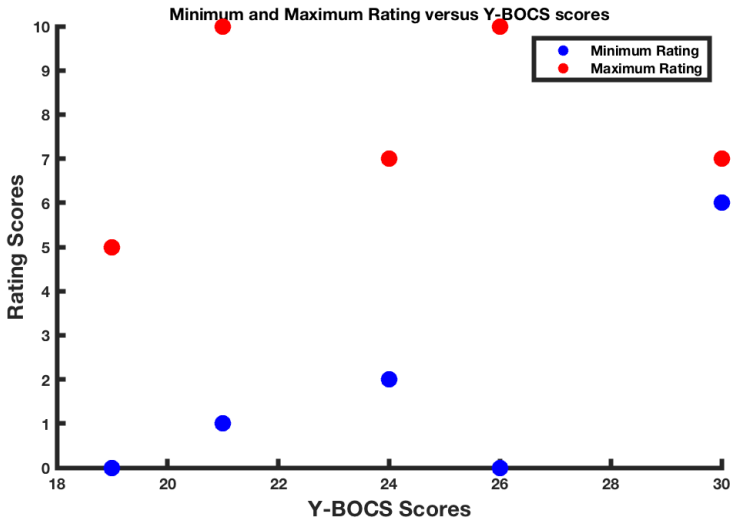


Figure 1. YBOC-S scores versus Maximum Rating. The patient with the lowest Y-BOCS score of 19 (ABV004) rated a maximum of 5, and the patient with the highest Y-BOCS score of 30 (ABV001) was continuously provoked for the entire length of the task, including the non-provoking object. This could be due to picking the incorrect non-provoking object. The rest of the three participants had Y-BOCS scores between this range and rated a maximum of 7, 10, and 10 respectively.

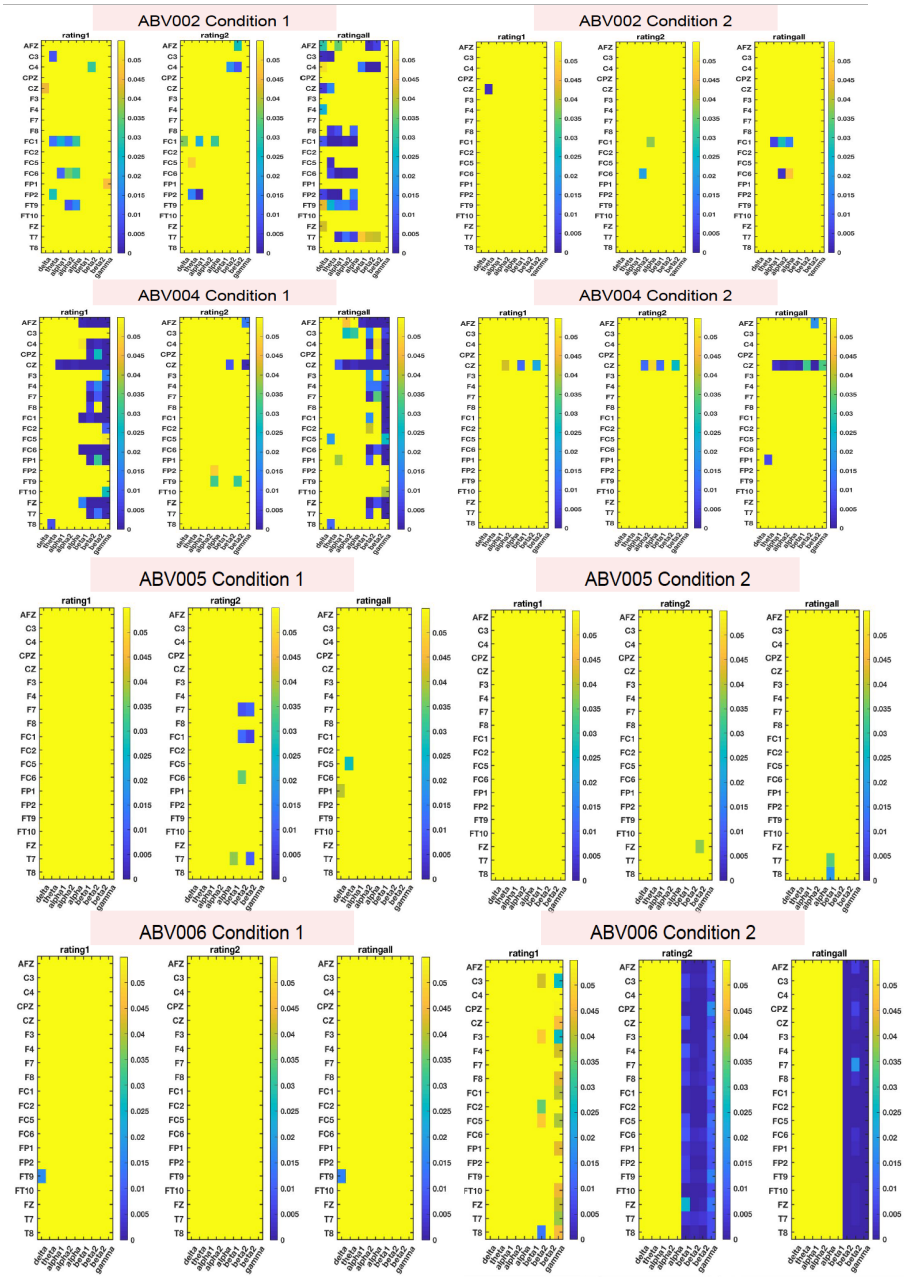
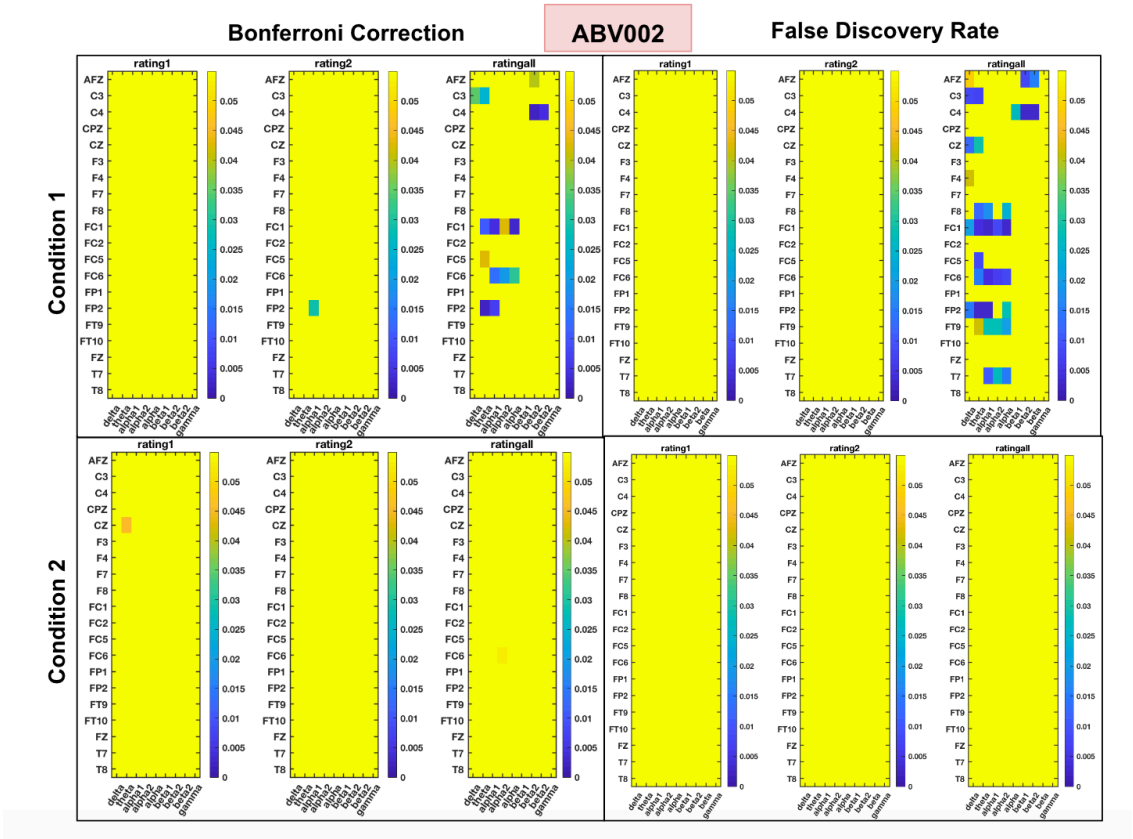
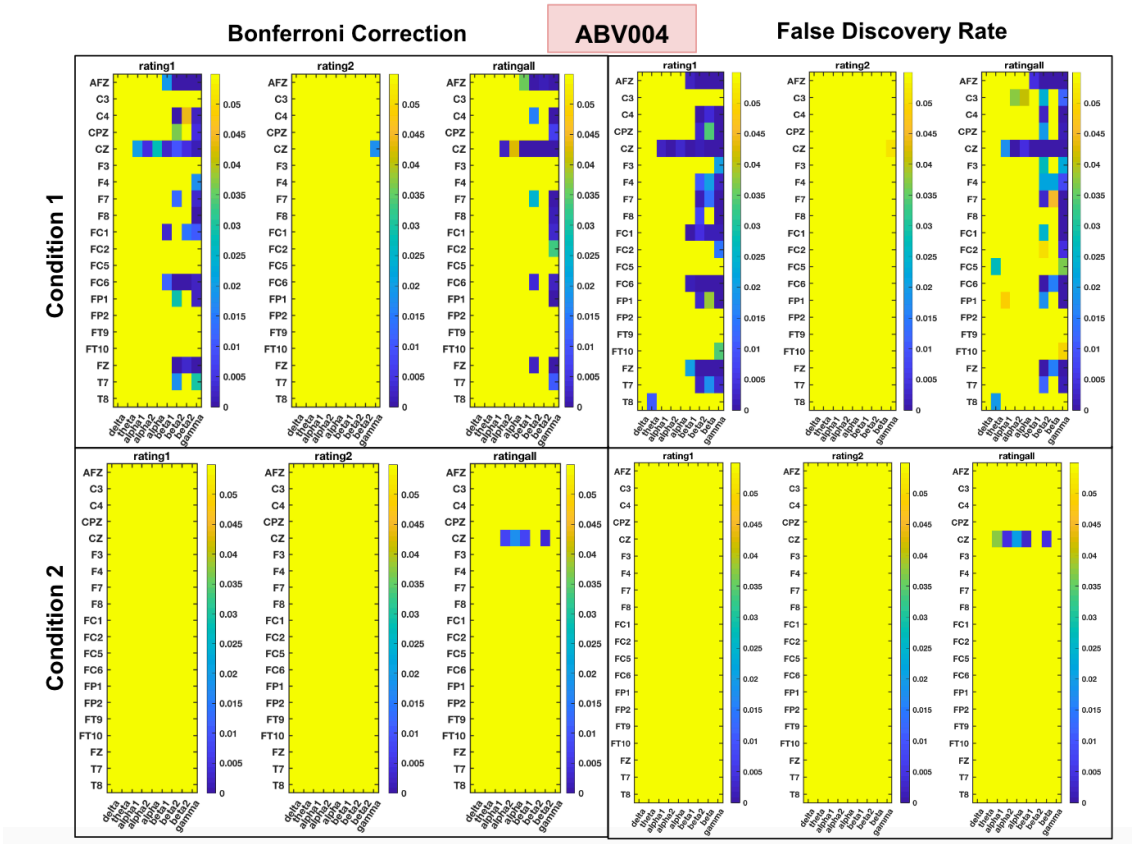
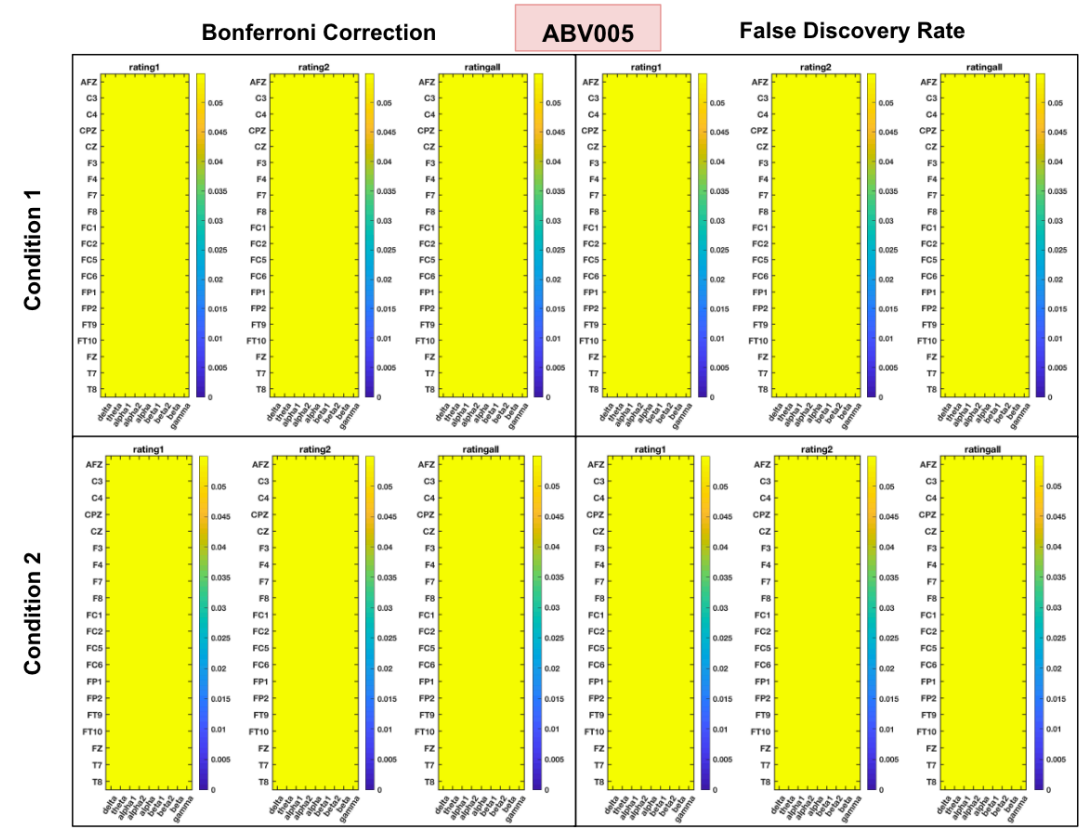


Figure 2. Multiplier Testing of Bonferroni with Test=18. 18 accounts for 9 frequency bands*2time periods. This shows the adjusted p-values with a smaller correction factor.


Bonferroni Correction
ABV002
False Discovery Rate
Condition 1
Condition 2
rating1
rating2
ratingall


Bonferroni Correction
ABV004
False Discovery Rate
Condition 1
Condition 2
rating1
rating2
ratingall


Bonferroni Correction
ABV005
False Discovery Rate
Condition 1
Condition 2
rating1
rating2
ratingall

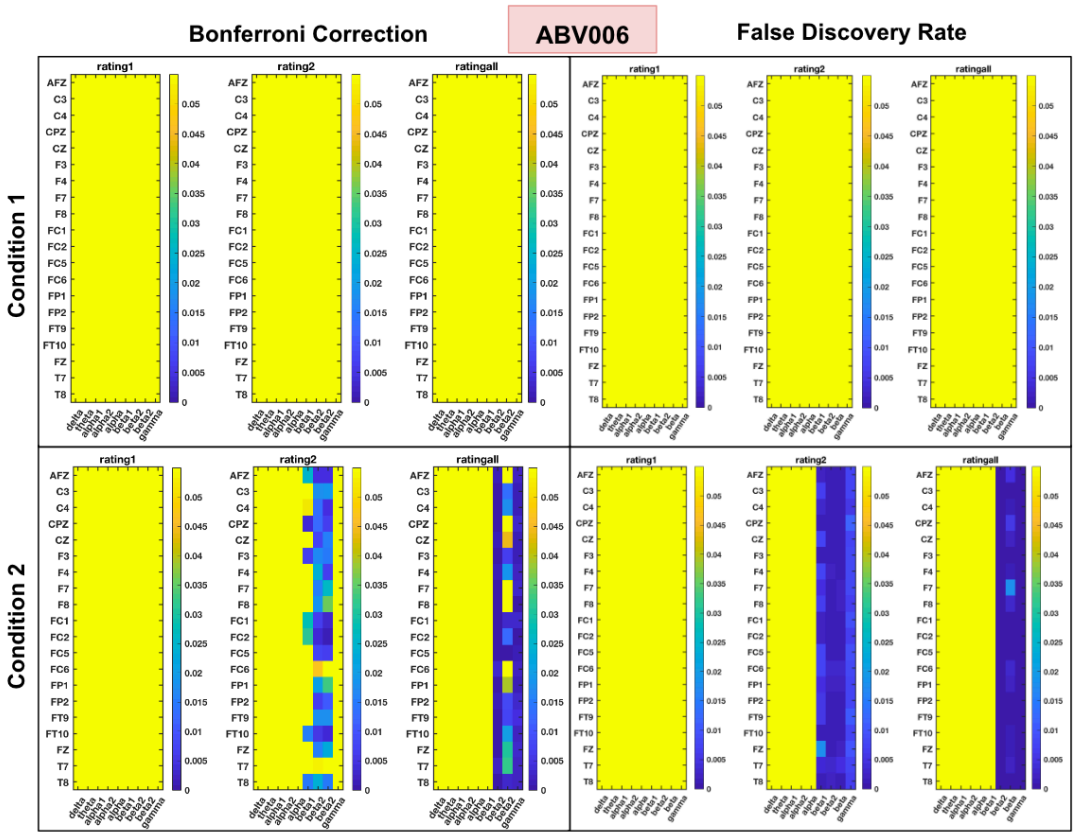

Bonferroni Correction
ABV006
False Discovery Rate
Condition 1
Condition 2
rating1
rating2
ratingall

Figure 3. Comparing Bonferroni Correction and False Discovery Rate, Benjamini-Yekutieli Procedure. The FDR test is less conservative than the Bonferroni Correction. There is no significant activity in ABV005 for both tests.

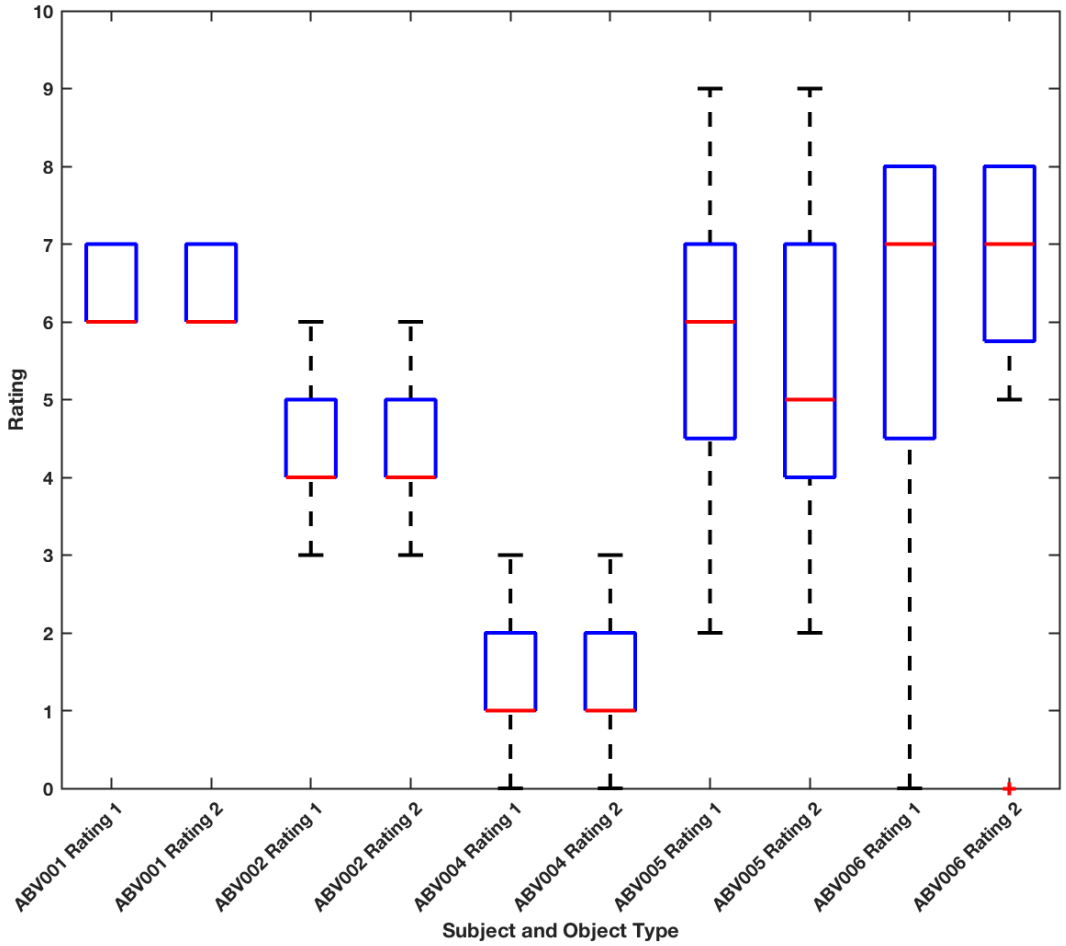


Figure 4. Summary showing rating 1 and rating 2 difference between all subjects for provoking object one. Ttest was performed between rating 1 and rating 2 distributions for all subjects and no significant difference was identified.

Description 1. Each statistical summary

The mean is the average of the dataset, and is equal to the sum of all the values divided by the number of values in the dataset. This means that if there are a few outliers in the data set, they will change the mean value because they are counted in the statistical summary and increase or decrease the number. The median is the middle value of the dataset,

meaning 50% of the data is larger and smaller than that value. The median is not as affected by outliers because if the bulk of the dataset is centered around a particular range, the median will be in that range. However, the median will not account for large variations in the data like the median and standard deviation. Standard deviation is the measure of variation in the dataset, and measures the average distance of each value in the data set from the mean in the dataset and is then divided by the number of values minus one in the dataset. It is useful in measuring the normal distribution for the dataset and indicates the range of a certain percentage of the dataset assuming normal distribution.

Description of False Discovery Rate (FDR), Benjamini-Yekutieli Procedure[69]

FDR is known to be less conservative than the Bonferroni correction. FDR controls for the number of discoveries that are false, or incorrect rejections instead of for the FWER by only controlling by the alpha value. First, the p-values are sorted from smallest to largest values. Then starting at the end with the largest values, the largest k, which is the number in the array, is calculated and determined by the value where $\frac{P(k)*m*c(m)}{\alpha} < k$. For this k value, anything smaller than the p-value at this point is rejected. P(k) is the p-value, m is the length of the sequence, and c(m) depends on whether the tests are independent or positively correlated.