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Resting-state Functional Connectivity Correlates of Inhibitory Control over Emotional Stimuli

Makayla Mattson
Northern Michigan University, makmatts@nmu.edu

RESTING-STATE FUNCTIONAL CONNECTIVITY CORRELATES OF INHIBITORY CONTROL OVER EMOTIONAL STIMULI

By

Makayla Lee Mattson

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RESTING-STATE FUNCTIONAL CONNECTIVITY CORRELATES OF INHIBITORY CONTROL OVER EMOTIONAL STIMULI

This thesis by Makayla Mattson is recommended for approval by the student's Thesis Committee and Department Head in the Department of Psychological Science and by the Dean of Graduate Studies and Research.

_____ _____
Committee Chair: Dr. Joshua Carlson Date

_____ _____
First Reader: Dr. Lin Fang Date

_____ _____
Second Reader (if required): Dr. Christina Hartline Date

_____ _____
Department Head: Dr. Adam Prus Date

_____ _____
Dr. Lisa Schade Eckert Date
Dean of Graduate Studies and Research

ABSTRACT

RESTING-STATE FUNCTIONAL CONNECTIVITY CORRELATES OF INHIBITORY CONTROL OVER EMOTIONAL STIMULI

By

Makayla Lee Mattson

Inhibitory control is defined as the stopping or overriding of a mental process with or without intention. It is known as a motor process in which executive control suppresses an automated motor response. Currently, there is no existing research discussing the neural mechanisms of an emotional anti-saccade task, therefore with the use of resting-state functional magnetic resonance imaging (fMRI) and an emotional anti-saccade task, this study aims to identify the neural correlates of inhibitory control over emotional stimuli. The anti-saccade task is known as an effective measure of inhibitory control since it requires inhibiting a reflexive response and re-orienting attention while emotional faces are presented. Given the nature of the anti-saccade, where it requires the top-down inhibition of an automatic pro-saccade response, investigating the neural correlates could serve as an important tool to evaluate deficits in response inhibition in clinical populations. Previous research was confirmed by demonstrating significant effects for the anti-saccade task. ROI-to-ROI analyses showed overlap in the salience and frontoparietal networks in relation to response inhibition. Seed-to-voxel analysis revealed significant connectivity between numerous seed networks in relation to response inhibition. Anti-saccade trials showed stronger functional connectivity between seeds (i.e. salience, default mode network, frontoparietal, and amygdala) compared to pro-saccade trials.

Keywords: Inhibitory control, emotional anti-saccade, functional connectivity

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Makayla Mattson

Department of Psychological Science

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Introduction

The format of this thesis follows the publication manual of the American Psychological Association (7th edition) and the Department of Psychological Science at Northern Michigan University. All people possess some degree of cognitive control which allows the flexibility to respond to the environment (Munoz & Everling, 2004). For example, while walking down a crowded sidewalk one might notice an attractive person in the distance. In most scenarios, looking towards that person and admiring how they look would be appropriate. However, if a person was walking alongside their partner, it might be wise to avoid looking in that direction and instead orient in the opposite direction. The ability to perform this behavior is a prime example of cognitive control and more specifically describes inhibitory control (i.e., a specific subtype of cognitive control). Inhibitory control allows people to respond automatically in one situation or contrarily allows suppression of automatic prepotent responses to instead perform an alternative response.

As research on inhibitory control has advanced, more recent theories suggest inhibitory-related processes are a family of functions rather than a single distinct construct (Friedman & Miyake, 2004). The present study discusses these newly theorized types of inhibitory control: cognitive inhibition, response inhibition, and emotional inhibition (Hung et al., 2018). However, there is minimal evidence supporting the separation of emotional inhibition from the other components of inhibitory control (i.e., cognitive inhibition and response inhibition). Given the lack of understanding of the interactions between inhibitory control and emotion processing regions, this study aims to identify the neural correlates of emotional inhibition. In particular, this study assesses the neural correlates of emotional inhibition using resting state functional magnetic resonance imaging (fMRI) and an emotional anti-saccade task.

Inhibitory Control

In cognitive neuroscience, inhibitory control is defined as the stopping or overriding of a mental process with or without intention (Gorfein & MacLeod, 2007). It is known as a motor process in which executive control suppresses a prepotent motor response (Bernal & Altman, 2009). Structurally, the prefrontal cortex (PFC) is widely known to be primarily responsible for executive function (Cipolotti et al., 2016). In the real world, inhibitory control is exemplified by students in a busy environment that are successfully capable of suppressing any urge to focus on the distracting environment around them while writing a paper. As discussed in Friedman and Miyake (2004), inhibitory control plays a key role in many mental operations such as attention, perception, memory, learning, language, action, and thought.

Inhibition-related functions have become a large focus within psychological research because of its relevance across a wide range of clinical populations. Deficits in inhibitory control processes have been observed in disorders such as attention deficit hyperactivity disorder (ADHD), autism, schizophrenia, obsessive-compulsive disorder (OCD), panic disorder, anxiety disorders, mood disorders, and alcoholism (Bernal & Altman, 2009; Friedman & Miyake, 2004; Hung et al., 2018). Changes in inhibitory functions have also been used to monitor the development of cognitive abilities, general lifespan development, or human maturation (Friedman & Miyake, 2004). In general, inhibitory control is crucial for performing normal daily tasks and when weakened, is known to lead to impulsive decision making. In order to attend to one of many concurrent events, it is important to be able to cognitively inhibit all other distracting stimuli.

As research on inhibitory cognition advances, proposed theories suggest inhibitory-related processes are a family of functions rather than a single distinct construct (Friedman &

Miyake, 2004). Noreen and MacLeod (2015) found no similarities or correlations between the think/no-think, go/no-go, memory retrieval, and Stroop tasks that all work to measure inhibitory control. This suggests that each task demonstrates different parts of the inhibitory process. Given these findings, it has been determined that the term "inhibition" has been overgeneralized and that researchers should be more specific when investigating inhibition (Friedman & Miyake, 2004; Stahl et al., 2014). Both Stahl et al. (2014) and Hung et al. (2018) discussed ways to separate out the possible components of inhibitory control, naming them response inhibition and cognitive inhibition. Additionally, emotional inhibition is thought to be another possible component of inhibitory cognition (Shafritz et al., 2006).

Processes of Inhibitory Control: Definition and Cognitive Mechanism

Cognitive Inhibition

Cognitive inhibition is defined as suppression of competing cognitive processing in order to solve relevant problems (Hung et al., 2018). It is classically measured using cognitive interference paradigms such as the Stroop and Flanker tasks that involve naming the color of colored words while ignoring conflicting word meanings (e.g., "Red" printed in the color blue). Or by responding to an arrowed flanker where there are distracting arrows pointing opposite of the correct response (e.g., < < > < < or > > < > > vs. < < < < < or > > > > >). In daily life, cognitive inhibition is exemplified by the previous example given of students who are successfully capable of suppressing any urges to focus on the distracting environment around themselves while writing a paper. They are suppressing any urge to process information from their environment so that they can attend to what is relevant to them.

Response Inhibition

Response inhibition is defined as suppression of a prepotent motor response to perform a different, more context-appropriate response (Hung et al., 2018). It traditionally is measured by paradigms such as go/no-go and stop-signal tasks that involve responding after the presentation of "go" targets or "response" signals, and withholding the responses when presented with "no-go" targets or "stop" signals. The anti-saccade task is similar in measuring response inhibition because it requires the top-down inhibition of an automatic pro-saccade response. The anti-saccade paradigm includes the presentation of a peripheral target where a correct response involves looking away to its mirror position (Munoz & Everling, 2004). Response inhibition can be described best by the previous example given where someone avoids looking at an attractive person because they are currently walking next to their partner. They are suppressing an automatic response to look at an attractive person and instead perform an alternative response by looking away from the attractive person because they are with their partner.

Emotional Inhibition

Emotional inhibition is defined as suppression of task-irrelevant and distractive emotional information (Hung et al., 2018). Emotional information is capable of enhancing or impairing behavioral performance and is dependent on how it interacts with the control functions (Pessoa, 2009). However, emotional inhibition specifically examines when emotional information is used as a distractor and is task-irrelevant. Emotional processing of task-irrelevant information is known to impede general cognitive processing due to how emotional information quickly catches attention unconsciously which leaves fewer resources available for cognitive control strategies (Dolcos & Denkova, 2014; Schimmack, 2005). In order to complete cognitive tasks containing emotionally salient information, the processing of task-irrelevant emotional

distractors must be suppressed (e.g., observing a target object while ignoring unpleasant pictures, or naming a word's ink color while disregarding its emotional meaning, etc.).

Emotional inhibition has been studied in a variety of cognitive tasks by including the addition of emotional stimuli (e.g. emotional flanker, emotional stroop, and emotional go/no-go) (Hung et al., 2018). Emotional anti-saccade tasks commonly include expressive facial stimuli (i.e. happy, sad, fearful, angry), neutral stimuli (i.e. no face, neutral face, car), and occasionally affective images (i.e. digitalized pictures). These types of emotional anti-saccade tasks have been researched in various clinical populations (e.g. social anxiety, attention deficit hyperactivity disorder, bipolar disorder) to characterize mechanisms such as executive function, eye-movements, and attention inhibition (Jiang et al., 2022; Kissler & Keil, 2008; Llamas-Alonso et al., 2020; Salvia et al., 2020; Yep et al., 2018).

Emotional inhibition has been researched as a distinct construct separate from response inhibition due to the unique neural processes that emotional distractors rely on (versus non-emotional ones) (Egner et al., 2008). Rebetez et al. (2015) observed an interaction and interference between emotional stimuli and response inhibition. Shafritz et al. (2006) found the same with cognitive inhibition, suggesting a dissociable relationship between all three. However, there is still minimal evidence supporting the separation of emotional inhibition from the other components of inhibitory control (i.e., cognitive inhibition and response inhibition) (Hung et al., 2018).

Processes of Inhibitory Control: Neural Mechanism

Functional magnetic resonance imaging (fMRI) is a tool used in neuroimaging that measures blood oxygenation level dependent (BOLD) changes in brain tissue between different regions. It is an imaging technique that does not require the use of injections, surgery, ingestion

of substances, or exposure to ionizing radiation. The measure is frequently corrupted by noise from various sources (i.e. movement), hence there are many statistical procedures used to extract the underlying signal. The resulting brain activation can be graphically represented via color-coded activation maps across the brain or specific regions studied. Event-related or task-based fMRI is used to detect connectivity between brain regions during exposure to a cognitive task or stimuli (Leuthardt et al., 2018). It is known to be advantageous because of its ability to observe differences in neural activity associated with individual events. Resting-state fMRI (rs-fMRI) is used to identify brain areas that are interacting in the absence of a stimulus or task. By measuring spontaneous neural activity, rs-FMRI is known to measure more default or baseline activation that reveals patterns of spontaneous neural activity and identifies resting-state networks (RSNs) that are consistently active across individuals (Crosson et al., 2010). Advantages of rs-fMRI includes the inclusion of participants who are less capable of participating in task-based studies (i.e. disabled, unconscious, children) in addition to greater simplicity in the data collection and analyses.

Hung et al. (2018) conducted a recent systematic meta-analysis of 66 fMRI studies (i.e. majorly task-based) that characterized all known neural systems that underlie the three inhibitory processes (i.e., cognitive inhibition, response inhibition, and emotional inhibition) (see table 1). The left anterior insula was the only region found across all three inhibitory processes and is explanatorily known as an important node in inhibition or executive control across many different paradigms (Cieslik et al., 2015; Nee et al., 2007; Xu et al., 2016). *Cognitive inhibition* consistently activates the dorsal frontal inhibitory system (i.e., dorsolateral prefrontal cortex, dorsal anterior cingulate, left inferior parietal lobe, and right superior/inferior parietal lobes). *Response inhibition* shows reliable activation in the fronto-striatal system (i.e., dorsal anterior

cingulate region and extended supplementary motor areas), the dorsal and ventral lateral prefrontal cortex, midbrain regions, basal ganglia, and parietal regions. Brain activations observed during response inhibition tasks reflect mechanisms including attention, working memory, and response selection (Hung et al., 2018).

Response inhibition, specifically within the anti-saccade task, includes neural regions that can be thought of in terms of visual fixation and saccadic eye movements (Munoz & Everling, 2004). A substantial amount of literature including lesion studies, human behavioral testing, functional neuroimaging, animal neurophysiology and detailed anatomy has identified several brain areas that are involved in controlling visual fixation and saccadic eye movements, including regions in the cerebral cortex, thalamus, superior colliculus, basial ganglia, brainstem reticular formation, and cerebellum. Peterburs et al. (2012) emphasizes the role of the cerebellum in saccadic eye movements by observing anti-saccade task performance in a population with cerebellar lesions. With the use of event-related fMRI and single-neuron electrophysiology, Ford (2009) confirmed the involvement of the caudate nucleus, basal ganglia, and frontal eye fields in an anti-saccade task (Ford et al., 2005).

The known neural correlates of *emotional inhibition* include the ventral inhibitory system (i.e. ventral surface of the inferior frontal gyrus and amygdala) (Hung et al., 2018). Shafritz et al. (2006) performed an event-related fMRI study with the use of emotional face stimuli modified in a go/no-go task (e.g. Happy-go, Sad no-go) and found that inhibition of responses to negative emotional stimuli activated additional brain regions, including inferior frontal/insular cortices, that were not observed in the regular non-emotional response inhibition stimuli. Schulz et al. (2009) conducted an event-related fMRI study using another modified go/no-go task with emotional stimuli and demonstrated an interaction between inhibition and

emotional processing in the partially dissociable limbic and frontocortical networks (i.e. inferior frontal gyrus, anterior insula, and amygdala). Current emotional inhibition literature is lacking for the neural correlates of an anti-saccade task over emotional stimuli. However, based on response and emotional inhibition literature, there is evidence supporting frontoparietal, salience, and default mode networks to be involved in the inhibition of emotional stimuli.

Table 1

Neural Correlates of Cognitive, Response, and Emotional Inhibition

Cognitive Inhibition		
Left middle/inferior frontal gyrus	Left inferior parietal lobe	Right cingulate gyrus
Right middle/inferior frontal gyrus	Right superior/inferior parietal lobe	Right supplementary motor area
Medial frontal gyrus	Right middle/inferior frontal gyrus	Left supplementary motor area
Cingulate gyrus	Left basal ganglia	Left anterior insula
Left anterior insula	Right inferior frontal gyrus	
Response Inhibition		
Right anterior insula	Right thalamus	Left inferior parietal lobe
Right basal ganglia	Midbrain (red nucleus)	Superior temporal gyrus
Right inferior parietal lobe	Supramarginal gyrus	
Emotional Inhibition		
Left anterior insula	Right amygdala	Right inferior/middle occipital
Inferior frontal gyrus	Left amygdala	

Note. Based on systematic meta-analysis (Hung et al., 2018)

This Present Study

Rationale

Given the lack of understanding of the interactions between response inhibition and emotion processing regions, this study aims to confirm the neural processes involved to further what is known about emotional inhibition. By using an anti-saccade task this study aims to confirm previous research by demonstrating significant effects of response inhibition (Munoz & Everling, 2004). Additionally, the neural correlates of an emotional anti-saccade task are

unknown and there is minimal existing resting-state functional connectivity (rsFC) research to this date. Functional magnetic resonance imaging is a tool used in neuroimaging that measures blood oxygenation level dependent (BOLD) changes in brain tissue between different regions. By using rs-FC to measure consistent spontaneous neural activity across participants, possible baseline neural correlates of response inhibition can be identified. With the addition of an emotionally salient stimulus, this study seeks to observe the potential functional connectivity, cognitive, and neural mechanisms behind an emotional anti-saccade task.

Research Questions

Research Question 1. With the addition of emotional stimuli, does the anti-saccade task show significant effects across trial type and valence?

Research Question 2. What are the neural correlates of inhibitory control over emotional stimuli?

Hypotheses

Hypothesis 1. The anti-saccade task over emotional stimuli will show significant effects across trial type and valence. A main effect between saccadic latencies was expected (i.e. pro-saccade vs anti-saccade) in addition to a main effect between valanced stimuli saccadic latencies (i.e. happy vs neutral, disgust vs neutral).

Hypothesis 2. The neural correlates of inhibitory control over emotional stimuli will include frontoparietal, salience, and default mode networks.

Methods

Participants

A total of 43 participants were included in this study (Female = 29, M_{age} = 20.7, *SD* = 2.44, range: 18-28). Participants were recruited from emails sent to a random selection of

undergraduate and graduate students at Northern Michigan University. On a voluntary basis, participants completed a brief Qualtrics survey and were included in the study if they met inclusion criteria. Exclusion criteria was based on functional magnetic resonance imaging (fMRI) restrictions, and inclusion criteria was based on eye-tracking demographic needs (see Table 2).

Table 2

Inclusion and Exclusion Criteria for fMRI-Cognitive Study

Variable	Criterion	Inclusion or Exclusion	Measure to be Used
Age	≥ 18 and ≤ 42	Inclusion	Demographic Form
Handedness	Right handed	Inclusion	Demographic Form
Normal Vision	Normal or corrected to normal	Inclusion	Demographic Form
MRI Contraindications	Metal in the body that cannot be removed (e.g. shrapnel, pacemaker, permanent retainer)	Exclusion	MRI Screening Form
History of Head Injury	History of head injury (e.g. concussion)	Exclusion	MRI Screening Form
Neurological History	A known neurological disorder	Exclusion	MRI Screening Form
Claustrophobia	Anxious in enclosed/tight spaces	Exclusion	MRI Screening Form
Pregnant	Pregnant	Exclusion	MRI Screening Form

Note. Criterion is based on fMRI and demographic restrictions.

This sample is part of a larger data set in the Cognitive × Affective Behavior & Integrative Neuroscience (CABIN) Lab. Data collection started in November 2021 and concluded in December 2022. Participants were compensated $50 for full completion of this study and received partial payments for completing portions of the study. Funding was received from research grants awarded to the principal investigators of the CABIN Lab.

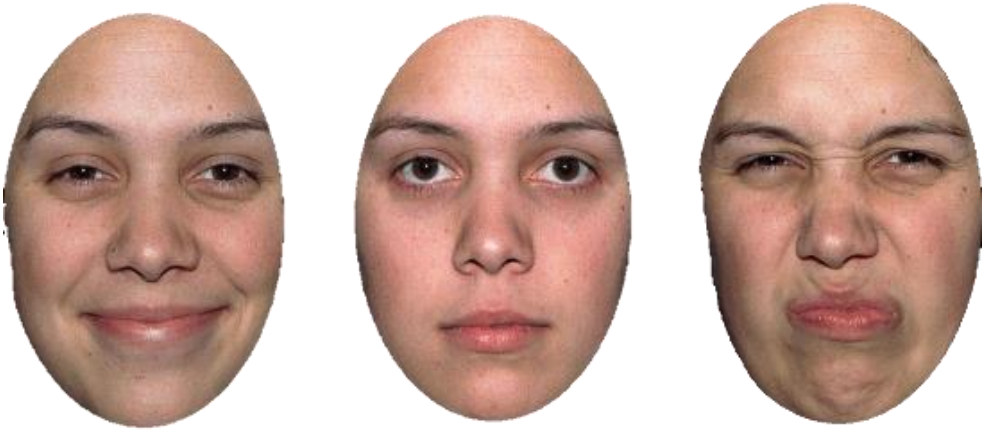
Materials

Emotional Anti-saccade Task

In order to measure response inhibition, a series of emotional anti-saccade trials were presented. Participants were presented with a series of randomized emotional stimuli selected from the NimStim Set of Facial Expression database (i.e., happy, neutral, or disgust faces; see Figure 1) (Tottenham et al., 2009). Before each block, participants were directed to look towards (pro-saccade) or away (anti-saccade) from the emotional stimuli (see Figure 2). At the start of each trial, participants were asked to focus on a red fixation cross in the center of the screen. Following the fixation cross, the emotional stimuli was presented on either the far right or far left of the screen and participants were to look towards or away from the stimuli. The task started with six practice trials for each saccade condition. Following the practice trials, the task continued with six blocks of trials (i.e., three blocks for anti-saccade trials and three blocks for pro-saccade trials). There were 36 trials per emotion and 12 trials per valence type (i.e., happy, neutral, or disgust). Facial stimuli were alternately presented on the right and left of the screen for 600ms after 1500ms of the fixation cross, 500ms of a blank screen followed (see figure 3).

Figure 1

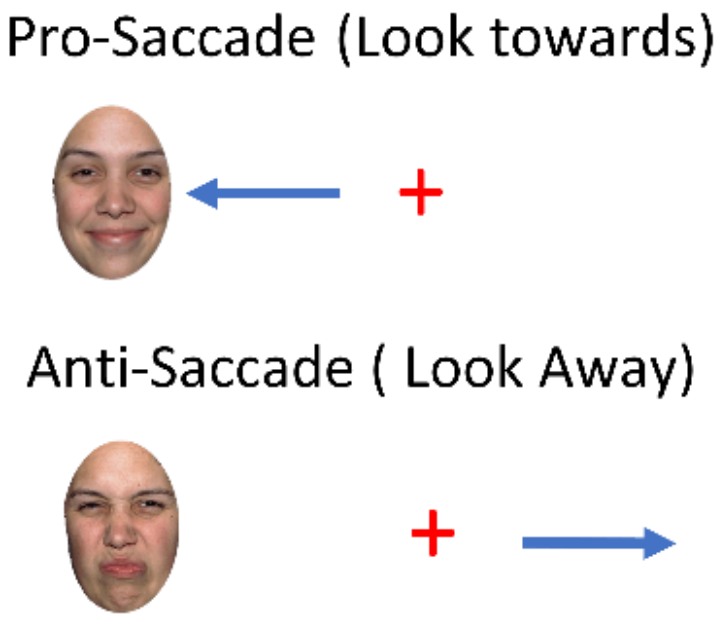
Emotional Stimuli



Note. Emotional stimuli included happy, neutral, and disgust faces. Images taken from the NimStim Set of Facial Expression (Tottenham et al., 2009).

Figure 2

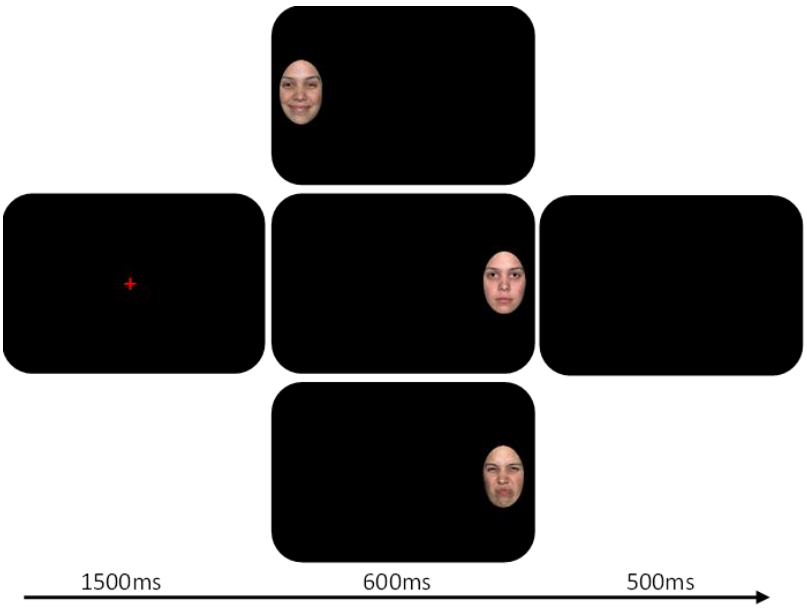
Procedure of Emotional Anti-saccade Task



Note. Before each block participants were directed to look towards (pro-saccade) or away (anti-saccade) from the emotional stimuli.

Figure 3

Timeline of the Emotional Anti-saccade Task



Note. Facial stimuli were presented on the screen for 600 ms after 1500ms of the fixation cross, 500ms of a blank screen followed.

Eye Tracking

Each participant's task performance was measured using an EyeLink Portable Duo (SR Research, Kanata, Ontario, Canada) system with a 1,000 Hz sampling rate. All participants were right-handed and had normal or corrected to normal vision. Gaze tracking of the right eye pupil was confirmed by calibration and validation at the beginning of the task as well as a drift detection before each trial.

fMRI

MRI scans were conducted at the UP Health System – Marquette location. A 1.5 Tesla General Electric whole-body scanner was used to collect high-resolution 3D FSPGR T2*-weighted functional images of participants in a resting state. The data were acquired and were

analyzed using standard preprocessing procedures such as those used in earlier CABIN Lab publications (Carlson et al., 2022).

Procedure

Participants were required to complete two separate sessions of the study: an eye-tracking session and MRI session. The eye-tracking session was held at Northern Michigan University in the eye-tracking lab and lasted no longer than two hours. In this session, participants were asked to complete eye tracking cognitive tasks along with several questionnaires. Proceeding the eye-tracking sessions participants provided their availability for the fMRI scanning session and completed that session within two weeks at UP-Health System in Marquette.

Data Analysis Preparation

Eye-tracking

Eye tracking data for the anti-saccade cognitive task were recorded in EyeLink Data Viewer (Version 3.1.97) where latencies were obtained for each participant. Regions of interest (ROI) were created for each trial and were located on the far right and left of the cue where the emotional stimuli were presented. Latencies for the first and last correct saccade start times were obtained. Anti-saccade and pro-saccade trial latencies were corrected to only include latencies greater than 80ms and less than 500ms. There were 12 practice trials (i.e. six for pro-saccade, six for anti-saccade) that were discarded from data analysis.

fMRI

Structural and functional MRI data were collected through a 1.5 Tesla General Electric whole-body scanner at the Upper Peninsula-Health System – Marquette hospital. MRI data were obtained within two weeks of completion of self-report measures. High-resolution 3D Fast

Spoiled Gradient Echo (FSPGR) T1-weighted images were collected using the following acquisition parameters: TR = 5.6 ms, TE= 2.1 ms, TI = 450 ms, flip angle = 9◦, FOV = 250, matrix = 256 × 256, voxel size = 0.98 × 0.98 × 1.2 mm. Participants underwent a 10-minute resting state scan, during which they were instructed to relax and remain awake for the entirety of the scan. 240 functional volumes were collected using the following T2 * weighted gradient echo pulse sequence: TR = 2500 ms, TE = 35 ms, flip angle = 90°, FOV = 220, matrix = 64 × 64, voxel size = 3.4 × 3.4 × 5 mm.

CONN (Version 19.c) was used to analyze all neuro-imaging data. All fMRI scans were uploaded into CONN and went through the pre-processing and denoising steps. The functional data were pre-processed using a flexible preprocessing pipeline (Nieto-Castanon, 2020b). The data were then realigned using SPM realign and unwarp procedure and resampled using b-spline interpolation to correct for motion and magnetic susceptibility interaction (Andersson et al., 2001). Temporal misalignment between different slices of the functional was corrected following SPM slice-timing correction (STC) procedure (Henson et al., 1999; Sladky et al., 2011). Lastly, functional data were smoothed using spatial convolution with a Gaussian kernel of 8 mm full width half maximum (FWHM). In addition, functional data were denoised using a standard denoising pipeline, followed by bandpass frequency filtering of the BOLD timeseries between 0.008 Hz and 0.09 Hz (Hallquist et al., 2013; Nieto-Castanon, 2020b).

Response inhibition was indexed by the difference between the anti-saccade means and the pro-saccade means (Anti - Pro) for all face conditions. Response inhibition scores and mean motion were entered into the model as covariates for ROI-to-ROI (Region Of Interest) connectivity analyses in CONN (version 19.c). All seed regions used in analysis were from the frontoparietal network, salience network, default mode network, and amygdala. Seed-to-voxel

analyses were also be conducted to explore connectivity beyond the networks used in the ROI-to-ROI analysis. Uncorrected and False-Discovery Rate (FDR) corrected *p* values were assessed for statistical significance of connectivity patterns ($\alpha = .05$).

Analytic Strategy and Expected Results

Hypothesis 1

The anti-saccade task over emotional stimuli will show significant effects across trial type and valence. A linear mixed model was performed using trial type (i.e. pro- vs anti-saccade), valence type (i.e. happy, neutral, or disgust faces), and the interaction of both trial type and valence type as independent variables. A main effect was expected between saccadic latencies (i.e. pro-saccade vs anti-saccade) where pro-saccade latencies would be shorter than anti-saccade latencies. Additionally, a main effect between valanced stimuli saccadic latencies (i.e. happy vs neutral, disgust vs neutral) was expected where face conditions (i.e. happy and disgust) would show overall increased latencies for both pro and anti-saccade trails compared to the neutral face condition.

Hypothesis 2

The neural correlates of inhibitory control over emotional stimuli will include frontoparietal, salience, and default mode networks. A multivariate general linear model was used to assess seed to voxel and ROI-to-ROI analyses. Uncorrected and FDR corrected p-values assessed statistical significance ($\alpha = .05$). The neural correlates of inhibitory control over emotional stimuli included frontoparietal, salience, and default mode networks. It was hypothesized that there would be significant functional connectivity between regions associated with attention (i.e. caudate nucleus, basal ganglia, and frontal eye fields), response inhibition (i.e. cerebellum, basial ganglia, superior colliculus, cerebral cortex, inferior parietal lobe, thalamus,

superior temporal gyrus, supramarginal gyrus) and emotional inhibition (i.e. amygdala, anterior insula, occipital gyrus, frontal gyrus, inferior frontal/insular cortices). The anterior cingulate cortex, left and right anterior insula, left and right prefrontal cortex, left and right supramarginal gyrus, left and right lateral prefrontal cortex, left and right posterior parietal cortex, medial prefrontal cortex, left and right amygdala, and left and right lateral preotic area were used as seeds in CONN to assess for the predicted effects.

Results

Data were collected from 43 participants; participants were excluded due to invalid fMRI scans (i.e. either due to excessive artifact or lack of completion) (n = 4), unsuccessful completion of the anti-saccade task (n = 1), or failure to meet latency inclusion criteria (n = 2). Thirty-six participants were included in data analysis (Female = 24, M_{age} = 20, SD = 2.59, range: 18-28).

Behavioral Data

The first aim of this study was to assess the effects of trial type and valence type on the latency of the first correct saccade in the anti-saccade task over emotional stimuli. A generalized linear mixed model was performed with latency of the first correct saccade imputed as the dependent variable. For the dependent variable, given that the shape of the distribution is negatively skewed, the following was used to transform the shape into positive skewed so that a gamma distribution could be used in the model. First, the maximum value of the dependent variable was found (i.e., 499). Then each dependent variable's value was subtracted from the maximum value plus one (i.e., 500), which made sure that all the values in the transformed distribution are larger than zero. The fixed effects included trial type (pro vs anti-saccade) and valence (disgust vs happy vs neutral). There was a significant main effect of trial type on latency of first correct saccade, $F(1, 8209) = 7169.64$, $p < .001$, where pro-saccade trials (M = 317.32,

SD = 23.40) showed shorter latency than the anti-saccade trials (*M* = 403.59, *SD* = 24.32). There was no significant effect of valence type, F(2, 8209) = .058, *p* = .944 an no interaction effect of trial type and valence, F(2, 8209) = .704, *p* = .495, see Table 3; Figures 4 and 5.

Table 3

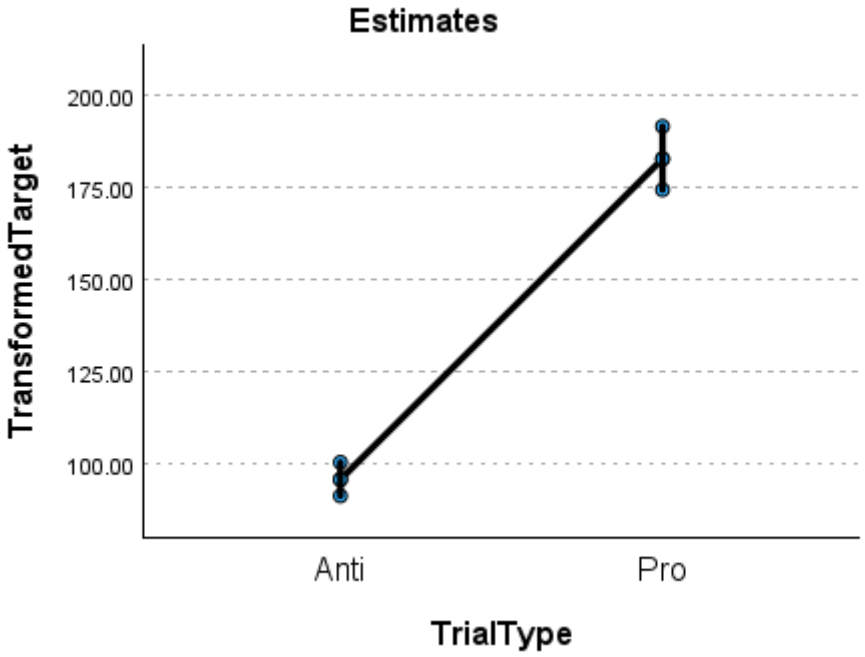
Average Latency and Standard Deviation for Valence x Trial Type

	Happy	Neutral	Disgust
Pro-Saccade	*M* = 316.72, *SD* = 23.11	*M* = 317.72, *SD* = 23.90	*M* = 317.53, *SD* = 24.97
Anti-Saccade	*M* = 402.45, *SD* =28.30	*M* = 403.89, *SD* = 24.10	*M* = 403.82, *SD* = 25.93

Note. There was no significant interaction effect of valence and trial type.

Figure 4

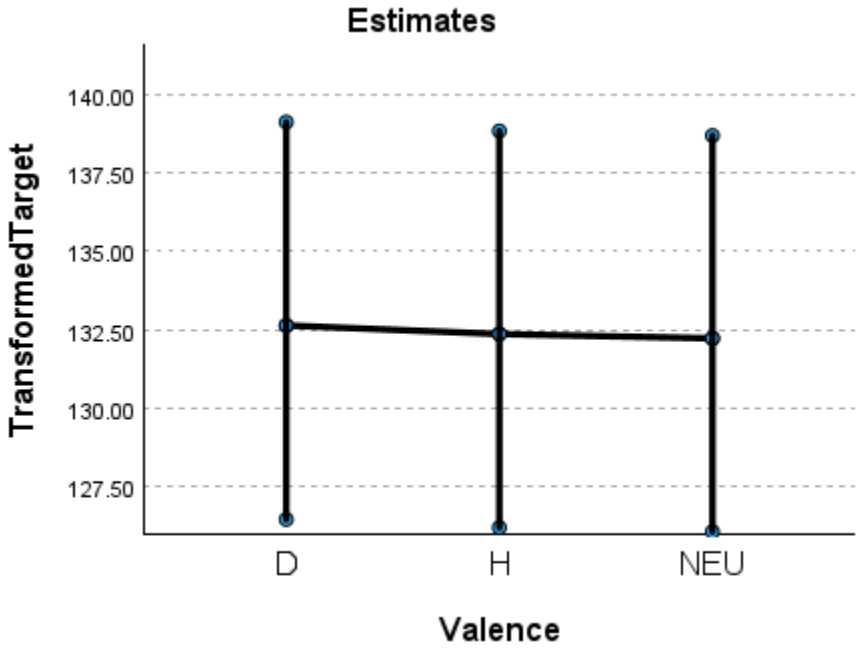
Significant Main Effect of Trial Type



Note. Anti-saccade (i.e. Anti) latency averages were significantly less than pro-saccade (i.e. Pro) latencies.

Figure 5

Insignificant Differences Between Valence Type



*Note. N*o significant difference of latencies between neutral (i.e NEU), disgust (i.e. D), and happy (i.e. H) stimulus trials.

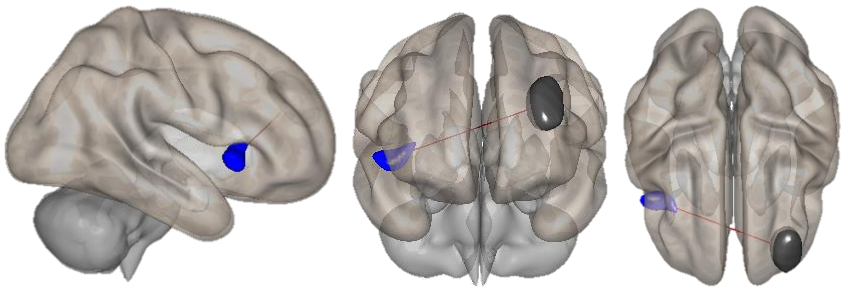
Due to the absence of a valence effect, the investigation into the neural correlates of emotional valence within the anti-saccade task was not continued. However, because there was an overall significant difference between pro- vs anti- saccade trial types, this study proceeded by assessing the neural correlates of general performance in the anti-saccade task. Therefore, the second hypothesis for this study shifted to assessing the neural correlates of response inhibition (i.e. not over emotional stimuli).

ROI-ROI Analysis

At an uncorrected level, ROI-to-ROI analyses showed two negative correlations between selected brain regions when comparing the difference between anti-saccade and pro-saccade trials among participants (see Figures 6 and 7). No corrected (FDR) correlations were found. Connectivity between the left rostral prefrontal cortex (x = -32, y = 45, z = 27) and the right anterior insula (x = 47, y = 14, z = 0), *p*-unc = 0.005 as well as the connectivity between the right posterior parietal cortex (x = 52, y = -52, z=45) and the right rostral prefrontal cortex (x = 32, y = 46, z = 27), *p*-unc = 0.026 was found to be associated with the response inhibition. Additionally, seed-to-voxel analyses showed many uncorrected results (see Appendix A).

Figure 6

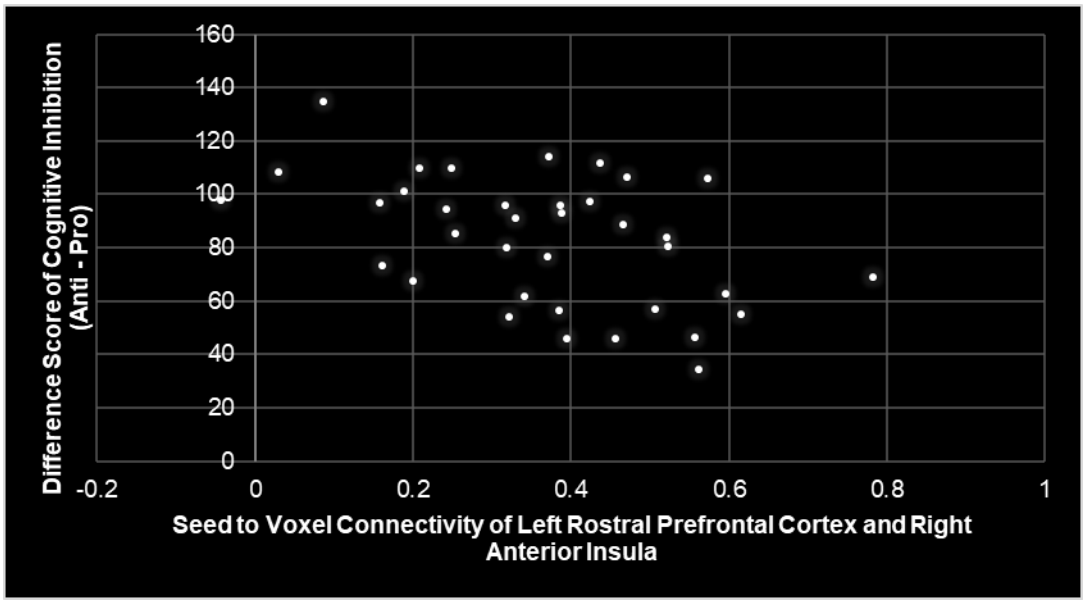
Connectivity Between Left Rostral Prefrontal Cortex and Right Anterior Insula



Note. Negative association shown.

Figure 7

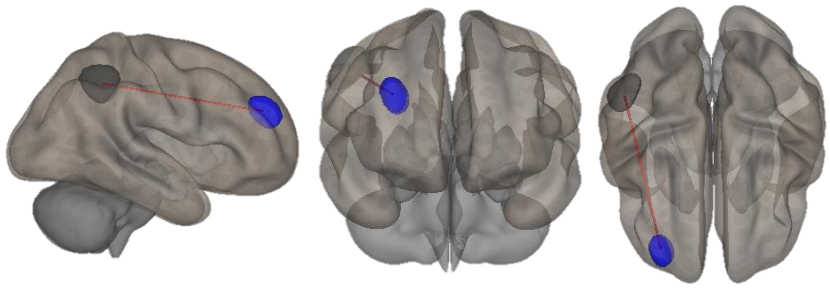
Scatter Plot of Correlation Between Response Inhibition and Functional Connectivity



Note. Negative correlation shown between difference score of response inhibition and seed to voxel connectivity between left rostral prefrontal cortex and right anterior insula.

Figure 8

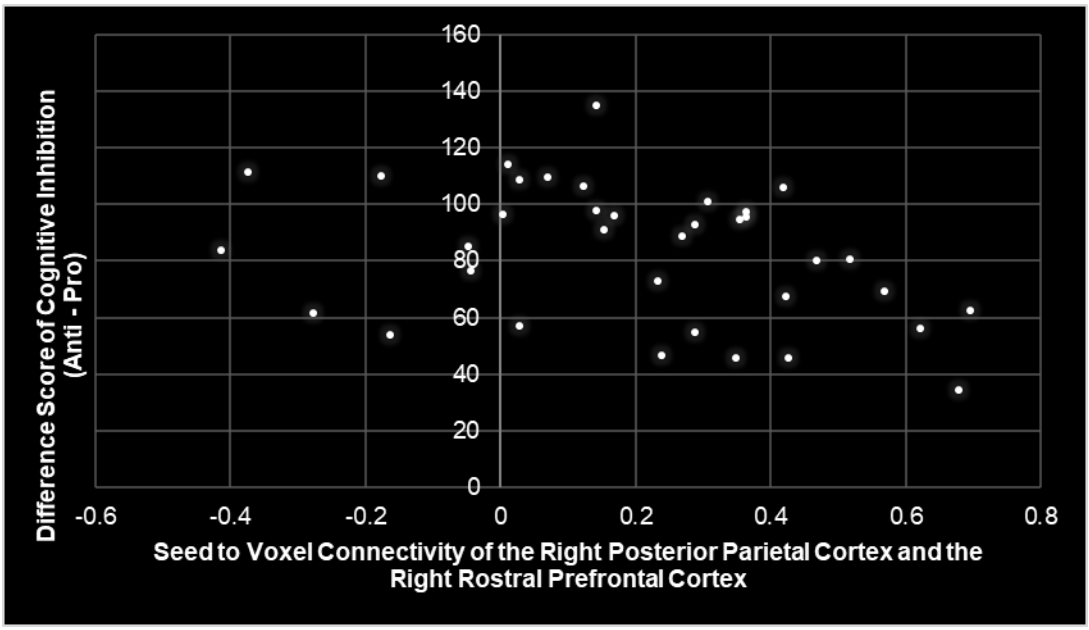
Connectivity Between Right Posterior Parietal Cortex and the Right Rostral Prefrontal Cortex



Note. Negative association shown.

Figure 9

Scatter Plot of Correlation Between Response Inhibition Functional Connectivity



Note. Negative correlation shown between difference score of response inhibition and connectivity between the right posterior parietal cortex and the right rostral prefrontal cortex.

Discussion

By demonstrating a difference between trial type (i.e. pro-saccade vs anti-saccade) there was an overall effect of response inhibition found for the anti-saccade task. There were no significant effects of valence which suggests limited efficacy of the emotional anti-saccade task used in this study to measure response inhibition over emotional stimuli. The neural correlates of individual differences in response inhibition were indexed by comparing anti-saccade and pro-saccade trials for both ROI-ROI and Seed-to-voxel rsfMRI functional connectivity analyses. ROI-to-ROI analyses showed overlapping connectivity between the salience and frontoparietal networks in relation to response inhibition. Seed-to-voxel analysis revealed numerous patterns of connectivity that were related to response inhibition (see Appendix A).

Behavioral Results

Hypothesis 1. The anti-saccade task over emotional stimuli will show significant effects across trial type and valence. A main effect between saccadic latencies was expected (i.e. pro-saccade vs anti-saccade) in addition to a main effect between valanced stimuli saccadic latencies (i.e. happy vs neutral, disgust vs neutral). The first hypothesis in this study was partially confirmed, as significant results were observed for trial type, but not for valence. There was a significant main effect of trial type on latency of first correct saccade, where pro-saccade trials showed shorter latencies than the anti-saccade trials. This finding is well supported in the literature surrounding the anti-saccade task (Coe & Munoz, 2017). Shorter latencies for pro-saccade trials provide insight into saccade suppression mechanisms. After the stimulus appears, performing an anti-saccade requires overriding the automated response (i.e., to orient towards the stimulus), this additional processing results in longer latencies. Response inhibition has been described as "stimulus interference" because it requires the suppression of competitive cognitive processing in order to perform an alternative response (Hung et al., 2018; Stahl et al., 2014). The anti-saccade task has consistently demonstrated significant effects of stimulus interference in task response which suggests that it is a valid measure of response inhibition (Coe & Munoz, 2017; Klein et al., 2010; Munoz & Everling, 2004).

We found no significant interaction between valence and trial type, revealing no significant differences between the happy, neutral, and disgust face conditions across pro-saccade and anti-saccade latencies. This finding was surprising because there is strong evidence that has exemplified how emotionally-arousing information tends to attract more viewing time (LaBar et al., 2000; Salvia et al., 2020). Salvia et al. (2020) carried out research demonstrating that social stimuli, like faces, capture and hold attention more effectively than other types of objects (i.e., cars). LaBar et al. (2000) designed a study using a free viewing task where neutral

pictures were paired with an emotional, unpleasantly arousing picture. When both stimuli were presented simultaneously, subjects' eye movements were shown to be affected by the emotional picture. This pattern has by now been replicated and extended to pleasant–neutral picture pairs (Kissler & Keil, 2008). In general, presented emotional (i.e. unpleasant and pleasant) pictures are known to be more likely to attract initial fixations than neutral pictures. However, unlike the anti-saccade task, these studies required stimulus competition given that there were two stimuli (i.e. one neutral, one emotional) that were competing for participants' attention. The anti-saccade task only presents distracting stimuli one per trial (i.e. one trial with neutral face, next with emotional). Perhaps in the absence of stimulus competition, any stimulus is salient and has bottom-up attention effects.

Llamas-Alonso et al. (2020) found the emotional anti-saccade effect to be significantly moderated by stimulus valence (i.e. angry and neutral face stimuli). Uniquely, Llamas-Alonso et al. (2020) included stop trials (i.e. looking at fixation while inhibiting reflexive response to look at a facial stimulus) which represented only the inhibition of an automatic response. It also randomized the order of pro-saccade, anti-saccade, and stop trials by presenting shapes to indicate to the participant what response was to be performed. The anti-saccade task in the current study used blocks of trials that were consistently either pro-saccade or anti-saccade trials. Kissler and Keil (2008) conducted an emotional anti-saccade task and observed that valence had a more pronounced effect when there was a gap period, during which the fixation point was removed 200 ms before the target appeared, marking yet another design variation compared to the current study. Yep et al. (2018) conducted an emotional anti-saccade task using emotional stimuli such as happy, neutral, sad, fearful, angry, or a face void of any facial features (i.e., no face) that acted as a control stimulus. An additional distinction between previously conducted

emotional anti-saccade tasks and the one employed in the current study is that the former utilized angry faces and a control no-face condition, while the latter used faces expressing disgust as the unpleasant valence type and neutral valence as the control. Additionally, in Yep et al. (2018) participants were directed to observe a centrally presented face and determine its gender. These differences in the design of the emotional anti-saccade task could potentially explain why there was not a significant effect of valence for the current study.

Functional Connectivity Results

Hypothesis 2. The neural correlates of inhibitory control over emotional stimuli will include frontoparietal, salience, and default mode networks. ROI-to-ROI analyses showed connectivity between salience and frontoparietal regions to be significantly correlated with response inhibition across different facial expressions. Prior research has established the involvement of these neural correlates in cognitive control and inhibitory processes. The findings of the current study extend this knowledge by demonstrating that variations in cognitive control among individuals are associated with distinct patterns of functional connectivity. When comparing anti-saccade and pro-saccade trials, seed to voxel analyses showed connectivity between seed regions such as the salience, frontoparietal, default mode, and amygdala networks with various networks within the brain. Specifically, the connectivity of the anterior insula, prefrontal cortex, superior temporal gyrus, amygdala, lingual gyrus, and cingulate gyrus were all found to be correlated with response inhibition and have been supported by previous research to be involved in inhibition.

ROI-to-ROI Analyses

The current study's framework is predicated on the variability among individuals, suggesting that individuals with increased connectivity between the left rostral prefrontal cortex and both the right anterior insula and the right posterior parietal cortex are likely to demonstrate

higher levels of cognitive control. The process of response inhibition demands a heightened effort to divert attention from a stimulus, which naturally explains the simultaneous robust activation in brain regions linked to multitasking and stimulus detection. Given the functions of these regions in steering attention, regulating spatial concentration, and creating spatial representations, it is clear that their increased interconnectivity would facilitate more efficient response inhibition.

The left rostral prefrontal cortex and the right anterior insula. There was a negative correlation between response inhibition (i.e. the difference between pro- vs anti-saccade latencies) and the connectivity between the left rostral prefrontal cortex and the right anterior insula. The negative correlation indicates that an increase in connectivity between the left rostral prefrontal cortex and the right anterior insula is associated with stronger response inhibition. The rostral prefrontal cortex (PFC) is known to be involved in executive function type processes such as inhibition (Dumontheil et al., 2008). According to Dumontheil et al. (2008) a number of theories of rostral PFC function have been proposed, attributing to this region a role in: episodic memory, multitasking, mentalizing, reallocation of attention, cognitive branching, self-referential evaluation or allocation of attention towards perceptually-derived or self-generated information.

The anterior insula (AI) has been recognized from early anatomical studies to be a multifaceted brain region (Uddin, 2015). The AI participates in visceral and somatic sensory processing, contributes to autonomic regulation of the gastrointestinal tract and heart, and is a motor association area (Augustine, 1996). As an important part of the salience network the anterior insula plays a key role in the detection of behaviorally relevant stimuli and responding to various salient signals (Wang et al., 2015). Additionally, the anterior insula is recognized for its significant contribution to inhibition or supervisory control within a range of interference

paradigms (Cieslik et al., 2015; Nee et al., 2007; Xu et al., 2016). The AI has been linked to all three types of inhibitory control (i.e. response, emotion, and cognitive inhibition) (Hung et al., 2018). The anterior insula, with its diverse array of functions, is believed to serve as an integrative component among the homeostatic, affective, and cognitive systems within the human brain (A. D. Craig, 2011; Kurth et al., 2010; Medford & Critchley, 2010; Menon & Uddin, 2010). Research indicates that the AI functions as an "internal outflow gate" in initiating and maintaining control mechanisms across task modalities and adjusting activity in task relevant brain regions by sending control signals to other brain regions (i.e. the PFC and downstream sensorimotor systems) to enable stable task performance as part of a salience network (Cieslik et al., 2015; Craig et al., 2010; Dosenbach et al., 2006, 2007; Menon & Uddin, 2010; Power & Petersen, 2013).

In interpretation, this correlation means that stronger functional connectivity between the left rostral PFC and the right anterior insula was associated with higher response inhibition. Response inhibition requires increased effort in directing your attention away from a stimulus so it is evident why stronger activation in regions associated with multitasking and stimulus detection would occur simultaneously. Increased connectivity between these two regions might be indicative of better cognitive processing, especially in terms of inhibitory mechanisms. The current study's design mirrors an approach based on individual variances, indicating that those with enhanced connectivity between the left rostral prefrontal cortex and the right anterior insula are likely to exhibit higher cognitive control levels.

The right posterior parietal and the right rostral prefrontal cortex. There was a negative correlation between response inhibition and the connectivity between the right posterior parietal and the right rostral prefrontal cortex. As mentioned above, the rostral prefrontal cortex

(PFC) is associated with executive functions like inhibition and is theorized to aid in episodic memory, multitasking, mentalizing, attention shifts, cognitive branching, and processing both external and internal information (Dumontheil et al., 2008). The posterior parietal cortex (PPC) has been identified to play a role in cognitive control, but has not been specifically identified as playing a role in inhibition (Huang et al., 2012). The PPC creates a spatial representation of surroundings, crucial for orchestrating motor actions with environmental objects (i.e. grasping). It is also believed to play a role in both obvious and subtle adjustments of spatial attention, which are important for saccadic eye movements. Additionally, the posterior parietal cortex has been shown to be associated with selective attention, memory retrieval, and mental calculation (Corbetta & Shulman, 2002; Dehaene et al., 2004; Derrfuss et al., 2005; Roberts & Hall, 2008; Wager et al., 2005).

This correlation demonstrates that stronger connectivity between the right posterior parietal and right rostral prefrontal cortex was associated with higher response inhibition. Considering the roles of these regions in directing attention, managing spatial focus, and forming spatial representations, it becomes evident that enhanced connectivity between them could contribute to more effective response inhibition. Increased connectivity between the right posterior parietal and right rostral prefrontal cortex could be a sign of more mental computation to satisfy attention needs. The present study's structure adopts a strategy that accounts for individual differences, suggesting that increased neural linkage between the left rostral prefrontal cortex and the right posterior parietal cortex may correlate with stronger cognitive control capabilities.

Clinical Implications

The anti-saccade task (AST) is widely used in experimental, clinical, and neuroscience research as a pronounced test of executive functions (Klein et al., 2010). It also has been used as a suitable marker for cognitive control decline in aging and Parkinsons's Disease patients (Ouerfelli-Ethier et al., 2018). With the addition of emotional stimuli, the AST has been used as a tool in characterizing emotion processing, in addition to executive functioning, in a variety of disorders including anxiety, disruptive behavior disorder, attention-deficit hyperactivity disorder, and bipolar disorder (Long et al., 2015; Myles et al., 2020; Yep et al., 2018). Additionally, AST has been used in previous literature assessing the impact that anxiety has on inhibitory control. Juangl et al. (2022) found that social anxiety (SAD) did not impair attention inhibition within the use of an emotional anti-saccade task. They found the SAD group exhibited a lower error rate compared to the healthy controls group, irrespective of the type of emotional face. Results of this study suggested that individuals with SAD might have better attention inhibition abilities than healthy controls and enhanced attention inhibition may underlie their avoidance of threatening social cues. Opposingly, without the use of social or emotional stimuli, Myles et al. (2020) found that impaired inhibitory control was correlated with trait and state anxiety and suggested that this effect is a well-established trend. Considering the debated link between anxiety and response inhibition, it would be advantageous to conduct this current study again with a group of individuals who have a high level of trait anxiety.

The current study can be used as a starting point for future research looking to assess the neural correlates of response inhibition in a clinical population. Resting state functional connectivity (rsFC) has proven many advantages that are specific to clinical populations. A large motivation for rsFC MRI is that it allows scientists to use broader samples of patients in different diseases. There are many clinical populations that are not easily capable of laying in an MRI

scanner, let alone capable of completing a task while in one. Functional MRI can be used in clinical applications to determine the brain abnormalities in a population of subjects with neurological disease. The brain is very active in resting-state without any stimuli where analysis of spontaneous fluctuations in BOLD signal are structured in spatial that are known as resting state connectivity networks (Reza Daliri, 2014). Mennes et al. (2012) used resting state functional connectivity to assess the correlates of inhibitory control in children with attention-deficit hyperactivity disorder. The results demonstrated the utility of rsFC approaches for assessing brain and behavior relationships in a clinical population.

This current study supports previous research on the role that the anterior insula plays as an identified neural correlate of response inhibition. Gilman et al. (2018) conducted a study assessing the neural correlates of inhibition in a sample of tobacco smokers. They found that individuals who quit smoking had greater neural activation in the anterior insula during NoGo trials specifically with smoking related cues. Crawford et al. (1996) found that patients with schizophrenia that had elevated error rates showed decreased activation in anterior insula relative to patients with normal anti-saccade performance. Similar to the current study, both studies infer that increased activation in the anterior insula is indicative of successful inhibition. This finding, that has already been replicated in two different clinical populations, could potentially be useful in the diagnosis and treatment of response inhibition deficits. Considering the current study's discovery that variations in cognitive control among individuals correlate with differences in resting-state functional connectivity (rsFC), and acknowledging that such individual differences manifest in clinical symptoms, it is reasonable to anticipate analogous neural underpinnings. However, additional studies are required to assess the extent of their generalizability.

Limitations

Sample Size

A major limitation for this study is the small sample size. In any study, larger power and sample sizes are necessary in order for the study to answer the research question(s) and then be able to make inferences about the population based on the results (Jones et al., 2003). Increasing the sample size is necessary for increased statistical power. The final sample size was 36 in this study due to limitations in funding and artifacts in the data. Based on the power analysis, the study was powered at .80 with an alpha of .05, aimed at detecting a correlation coefficient of ($r \geq$ 43). The overall scope of this study was impacted by the limited funding available, which was solely derived from internal sources; this, in turn, restricted the number of MRI sessions rented from the hospital and limited participant compensation.

Data were collected from 43 participants; four participants were excluded based on invalid MRI scans (e.g., due to excessive artifact resulting in less than 50% of remaining after motion correction). One participant was excluded from behavioral task incompletion (i.e. due to the eye-tracker not being able to recognize participant's pupils). Anti-saccade and pro-saccade trial latencies were corrected to only include latencies greater than 80ms and less than 500ms. Previous research has suggested removing latency outliers that are not within a reasonable timeframe for completing task saccades (Polden & Crawford, 2023). Based on this criteria, two participants were excluded due to having less than 17% of valid anti-saccade trials. The remaining 36 participants were used in the final data analysis.

Generalizability

It is important to acknowledge details on the lack of diversity of the sample and the convenience sampling method used in this study. The sample contained primarily young adult females: 80% being female (n = 29) with ages ranging between 18-28. The method used for

sampling is considered a non-probability sampling method, which means that the participants were gained based on availability and proximity to the campus, lab, and university area. Due to this, the current sample cannot be generalized into a clinical sample as it is not representative of a population. Consequently, the results obtained may only apply to the current participants or a young adult/student population (Elfil & Negida, 2017). It is important to investigate the same research questions in larger more diverse samples because the results would be subject to less bias and have the ability to be generalized outside of the participant group (Stratton, 2021). Subsequently, results obtained from a broader and more varied sample, including clinical populations, could potentially enhance the generalizability of the findings.

Methods and Results

Currently there is a large range of neural correlates that are thought to be involved in inhibition (Hung et al., 2018). Additionally, there is limited resting state functional connectivity research investing the neural correlates specific to the anti-saccade task and emotional inhibition. With this lack of prior studies, this current study uses regions of interest (ROI) that have been found to be involved in inhibition and are not necessarily known to be specific to the anti-saccade task or emotional inhibition. Generally, the less ROIs the stronger (i.e., greater statistical power) the model (Whitfield-Gabrieli & Nieto-Castanon, 2012). As research involving the specific types of inhibition advances, ROIs can be narrowed down to strengthen the models for functional connectivity analysis. Although limiting the number of ROIs strengthens the model's statistical strength, it restricts the number of ROIs that can be used and therefore may overlook important rsFC patterns occurring outside the selected ROIs. The use of exploratory seed-to-voxel analyses partially compensates for this by allowing ROIs to be assessed for connectivity

with the entire brain. However, this means that connectivity between two regions that were not selected as ROIs could still not be found.

This current study found a variety of uncorrected cluster level p-values (p-unc). This statistic is defined as the likelihood under the null hypothesis of a randomly selected pair of networks showing equal or larger effects than those observed between this pair of networks (Nieto-Castanon, 2020). These uncorrected values are computed by comparing the mass of a given cluster with the observed distribution of cluster mass values across all clusters observed in the permutation/randomization iterations. Cluster level FDR-corrected p-values are defined as the expected proportion of false discoveries among all clusters of this or larger size over the entire analysis volume, again under the null hypothesis. Uncorrected p-values are known to be appropriate when the researcher's original hypotheses involve only the connectivity between two ROIs and FDR-corrected p-values are appropriate when the researcher's original hypotheses involve the connectivity between larger sets of ROIs and do not specify which ROIs are expected to show an effect (Whitfield-Gabrieli & Nieto-Castanon, 2012). Given the hypotheses in this current study, FDR-corrected p-values would be necessary to show an effect. Therefore, the uncorrected results found in this current study require further investigation to confirm significance and must be interpreted with caution.

Strengths

Emotional Anti-Saccade Task

The emotional anti-saccade task has shown to be an understudied behavioral measure for inhibition. Many studies have proved the validity of the anti-saccade for measuring attention redirection or inhibition (Coe & Munoz, 2017). Creating a task that successfully integrates emotion and inhibition would be a groundbreaking advancement in cognitive control research.

This study contributes to the literature by demonstrating a method of performing the emotion anti-saccade task and suggesting ways to improve it for future research (see directions for future research below).

Resting-state Functional Connectivity

Given that rsfMRI is used to identify brain areas that are interacting in the absence of a stimulus or task, it is advantageous because it allows the inclusion of participants who are less capable of participating in task-basted studies (i.e., disabled, unconscious, children). Uniquely, rsFC is a valid measure of baseline activation which reveals patterns of spontaneous neural activity and identifies resting-state networks (RSNs) that are consistently active across individuals (Crosson et al., 2010). The brain is very active in a resting-state without any stimuli, where recent research as demonstrated that spontaneous modulation of the BOLD is not produced randomly (Reza Daliri, 2014). Hence, rsFC has proven very valuable in the clinical area of fMRI applications. Given that lack of existing literature, this study adds insight on the resting-state functional connectivity (rsFC) of an emotional anti-saccade task.

Directions for Future Research

Given the lack of research studying the neural correlates of an emotional anti-saccade task, future research is needed to advance the quality of the task and the understanding of the neural processes behind it. Since the anti-saccade task has been established as a useful measure of cognitive control, future research should aim to increase the amount of resting state data for the anti-saccade task. Replicating this study with a larger sample sized and finding corrected p-values would allow this advancement of the known resting state networks of inhibition. In terms of the emotional anti-saccade task, this current study reveals that adjustments in integrating emotion into the task might need to be made. Suggested improvements include randomizing

valence trials, increasing the noticeability of valence (i.e. making face bigger, closure to the que, etc.), and trying alternative emotional stimuli (i.e. images, film clips).

Overall, this current study would be best replicated with the use of a larger sample and within a clinical population. Given the controversy of the relationship between anxiety and response inhibition, replicating this study within a sample of high-trait anxious individuals would be beneficial.

Conclusion

Response inhibition is a neuropsychological process by which executive control suppresses or contains inappropriate behavioral responses. The anti-saccade task is known as an effective measure of cognitive control since it requires inhibiting a reflexive response and re-orienting attention while emotional faces are presented. With the use of resting-state functional connectivity, the neural correlates of response inhibition were assessed in this study. Previous research was confirmed by demonstrating significant differences between pro-saccade and anti-saccade trials showing an effect for the anti-saccade task. There were no significant effects when comparing valence differences suggesting limited efficacy of response inhibition over emotional stimuli. ROI-ROI analyses showed connectivity between the left rostral prefrontal cortex and the right anterior insula and connectivity between the right posterior parietal and the right rostral prefrontal cortex to be negatively correlated with response inhibition. Consistent with earlier findings, increased activation in the anterior insula was found to be indicative of increased inhibition which may prove to be extremely beneficial for diagnosing and treating deficits in response inhibition. However, uncorrected results were found within these analyses therefore further investigation to confirm significance is necessary and results must be interpreted with caution. By replicating this study in a larger sample and within a clinical population corrected significant and increased generalizability could likely be achieved.

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APPENDIX A

Seed to Voxel Results

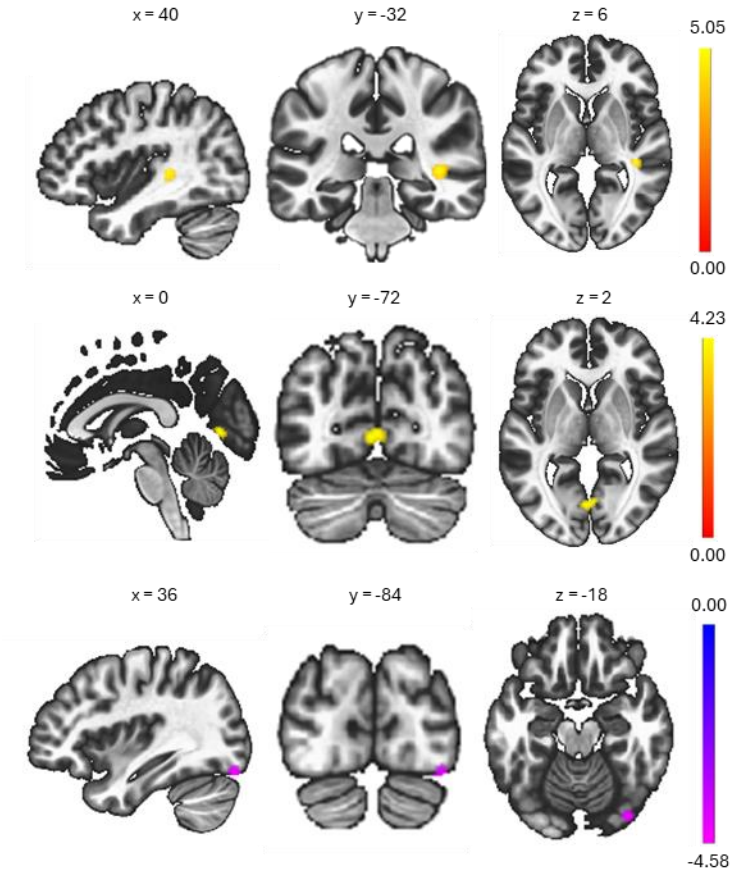
Many uncorrected significant correlations were found when comparing the differences between anti-saccade and pro-saccade trials through Seed-to-Voxel analyses. At an uncorrected p-unc < .05 level, there was a positive correlation between the difference of anti-saccade and pro-saccade trials and the connectivity between the right lateral parietal cortex and a cluster near the superior temporal sulcus extending into the adjacent white matter (x=40, y=-32, z=2, *p*-unc = .035, k = 55). There was a similar positive correlation between the left amygdala and the lingual gyrus (LG) (x=-2, y=-72, z=4, *p*-unc = .024, k = 74) and a negative correlation between the right rostral prefrontal cortex (RPFC r) and the right inferior division of the lateral occipital cortex (lLOC r, x=36, y=-82, z=-18, *p*-unc = .048, k = 59, see figure 8). Additionally, there was a negative correlation between the difference of anti-saccade and pro-saccade trials and the connectivity between the left anterior insula and the brainstem (x = 8, y= -6, z=-30, *p*-unc = 0.008, k = 114) (see figure 9).

Further Seed-to-Voxel analyses comparing the differences between anti-saccade and pro-saccade trials found more than one correlating voxel at the uncorrected level. Connectivity between the right anterior insula was negatively correlated with four separate voxels: left Heschl's Gyrus (x =-50, y=-18, z=0, *p*-unc = 0.004, k = 114), Superior Temporal Gyrus (x=62, y=-12, z=-04, *p*-unc = 0.006, k =121), right planum temporal (PT r, x=56, y=-24, z=14, *p*-unc = 0.043, k = 121), and right frontal orbital cortex (z=18, y=20, z=-22, *p*-unc = .046, k = 55, see

figure 11). When comparing the difference between the pro-saccade and anti-saccade trials, the connectivity between the left lateral parietal cortex was negatively correlated with two individual voxels: right frontal orbital cortex (x=20, y=32, z=-08, *p*-unc = 0.021, k = 88) and paracingulate gyrus (PaCiG l, x=-04, y=30, z=38, *p*-unc = 0.021, k = 85, see figure 13). When comparing the difference between anti-saccade and pro-saccade trials, the rsFC between the right lateral prefrontal cortex was found to be negatively correlated to the left intracalcarine cortex (ICC l, x =-8, y=-76, z=10, *p*-unc = 0.009, k = 64) and positively correlated to the right frontal pole (FP r, x=18, y=46, z=-16, *p*-unc = 0.028, k = 72, see figure 14). The connectivity between the left lateral prefrontal cortex (LPFC l) was negatively correlated with two voxels: the anterior division of the cingulate gyrus (AC, x=2, y=34, z=4, *p*-unc = 0.038, k = 64) and the left paracingulate gyrus (PaCiG l, x=-06, y=30, z=36, *p*-unc = .014, k = 95, see figure 15).

Figure 10

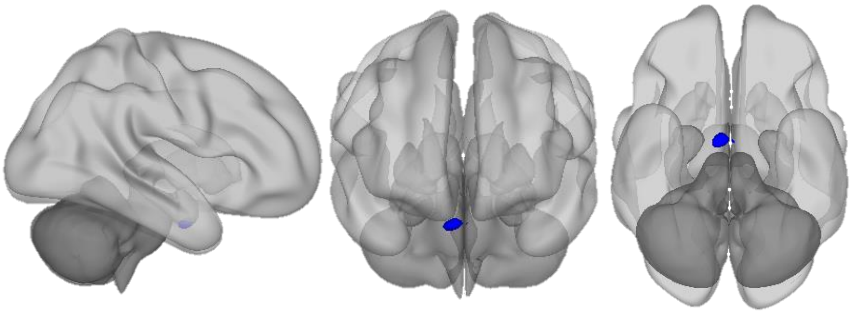
Three Significant Seed-to-Voxel Clusters



Note. From top to bottom voxel clusters are displayed: positive correlation between the right lateral parietal cortex and the white matter near the superior temporal sulcus, positive correlation between the left amygdala and lingual gyrus (LG), and negative correlation between the right rostral prefrontal cortex (RPFC) and the inferior division of the lateral occipital cortex (lLOC r).

Figure 11

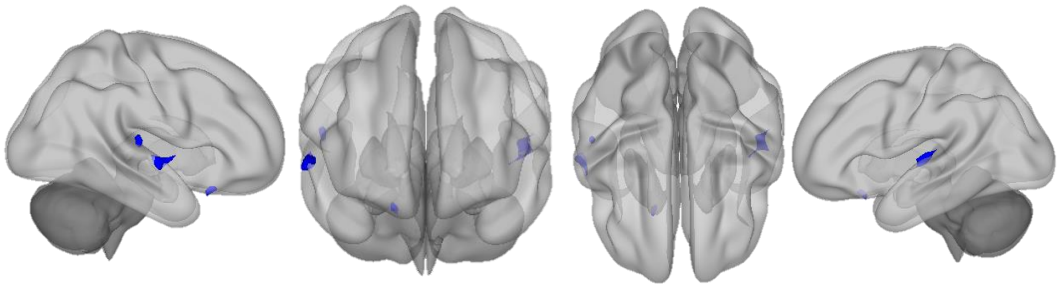
Connectivity Between the Left Anterior Insula and the Brainstem



Note. Negative connectivity with the brain stem cluster is shown.

Figure 12

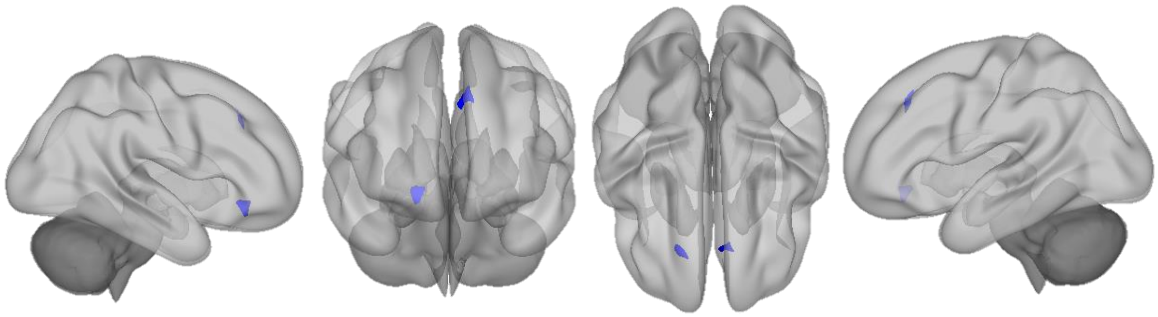
Connectivity Found with the Right Anterior Insula



Note. Significant clusters include negative connectivity with Heschel's gyrus left (HG l), right posterior division of the superior temporal gyrus (pSTG r), right planum temporal (PT r), and the frontal orbital cortex right (FOrb r).

Figure 13

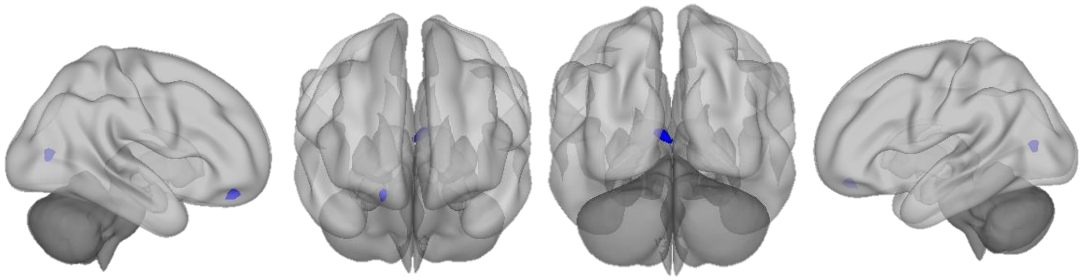
Connectivity Found with the Left Lateral Parietal Cortex



Note. Significant clusters include negative connectivity found with the right frontal orbital cortex (FOrb r) and left paracingulate gyrus (PaCiG l).

Figure 14

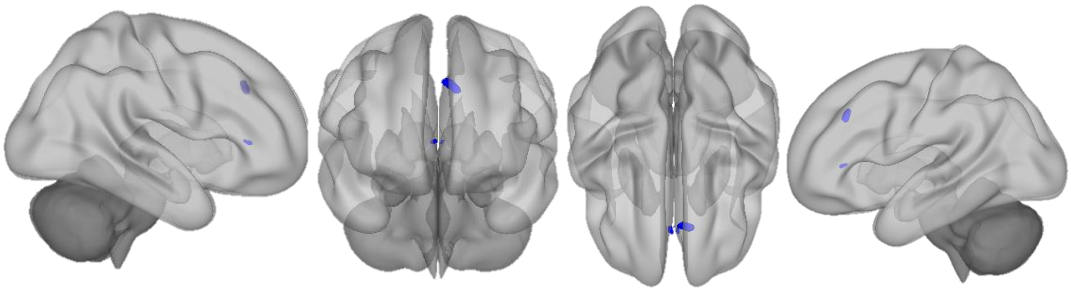
Connectivity with the Right Lateral Prefrontal Cortex



Note. Significant clusters include negative connectivity found with the left intracalcarine cortex (ICC l), right frontal pole (FP r).

Figure 15

Connectivity with the Left Lateral Prefrontal Cortex



Note. Significant clusters include negative connectivity found with the anterior division of the cingulate gyrus (AC), and the left paracingulate gyrus (PaCiG l).

APPENDIX B

IRB Approval Form

NORTHERN MICHIGAN UNIVERSITY

Graduate Studies and Research
Marquette, MI 49855-5301
906 227 2300
www.nmu.edu/graduatestudies/

MEMORANDUM

TO: Joshua Carlson
Lin Fang

Makayla Mattson
Morgan Oja
Psychological Sciences Department

DATE: September 3, 2022

FROM: Lisa Schade Eckert,
Dean of Graduate Studies and Research

RE: Modification to HS20-1156
Original IRB Approval Date: 12/7/2020
Modification Approval Date: 9/3/2022
"R15MH110951: Neuroplasticity in an Extended Amygdala Network as a Target Mechanism for Attention Bias Modification Outcome (Specific Aim 1)"

Your modification for the project "R15MH110951: Neuroplasticity in an Extended Amygdala Network as a Target Mechanism for Attention Bias Modification Outcome (Specific Aim 1)" has been approved by the Northern Michigan University Institutional Review Board. Please include your proposal number (HS20-1156) on all research materials and on any correspondence regarding this project.

Any additional personnel changes or revisions to your approved research plan must be approved by the IRB prior to implementation. Unless specified otherwise, all previous requirements included in your original approval notice remain in effect.

Until further guidance, per CDC guidelines, the PI is responsible for obtaining signatures on the COVID-19 Researcher Agreement and Release and COVID-19 Research Participant Agreement and Release forms.
If you have any questions, please contact the IRB at hsrr@nmu.edu.

APPENDIX C

Photo Release Form

The photo release form has been submitted independently.