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The effects of perceived discrimination on the resting state connectivity of the brain in older adults

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THE EFFECTS OF PERCEIVED DISCRIMINATION ON THE RESTING STATE CONNECTIVITY OF THE BRAIN IN OLDER ADULTS

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ABSTRACT

Over the last 20 years, there has been increasing research on the negative effects of discrimination on the mental and physical health of people of color. As mental health has an important relationship with the functional connectivity of brain networks, it is vital to further understand this. One way to measure functional brain connectivity is by observing the activity of the brain's resting state networks (RSN) while a participant is at rest. Previous studies investigating connectivity have demonstrated a relationship between altered connectivity of RSNs and neuropsychiatric disorders, including Alzheimer's disease, depression, and anxiety. The RSN of interest in this analysis is the salience network (SN). This network, anchored in the anterior insula and dorsal anterior cingulate cortex, is involved in the responses to "salient" stimuli that are infrequent in space or time, compete for an individual's attention, and are surprising or emotionally engaging, such as an act of discrimination. The aim of this study was to use a seed-based correlation analysis to examine the relationship between perceived discrimination and the functional connectivity of the SN in black and white participants and to evaluate the differences in SN functional connectivity between black and white participants. Resting state functional connectivity was measured by using the functional magnetic resonance imaging (fMRI) data collected from 18 healthy older adults partaking in two different

studies investigating aging, cognition, and the accompanying changes in neuroanatomy. The Analysis of Functional NeuroImages (AFNI) software was used to examine the correlations in activation in the primary nodes of the SN with activation in clusters in the other primary nodes. Perceived discrimination was measured using the Experiences of Discrimination Scale (EOD), a self-report measuring the frequency of instances of discrimination and the perceived reason behind the discrimination. Preliminary results from this analysis demonstrated that black participants, when compared to the white participants, demonstrated greater functional connectivity between the left and right insula and decreased functional connectivity between the right anterior cingulate cortex and the right insula. Black participants demonstrated a positive association between perceived overall discrimination and functional connectivity between the right and left insula and a negative association between perceived overall discrimination and functional connectivity between the right anterior cingulate cortex and the left insula. The white participants demonstrated a negative association between perceived overall discrimination and functional connectivity between the left and the right insula. Considering the inability for these results to survive correction for multiple comparisons, a larger sample size is necessary to obtain true statistical significance. Although existing research has implicated functional connectivity changes in the regions of the salience network in populations experiencing social exclusion, anxiety, and depression, further analyses are necessary to expand the limited research available regarding the effects of overall and race-based discrimination on the resting state functional connectivity of neural networks involved in emotional processing.

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LIST OF ABBREVIATIONS

AARG……..……..Alzheimer's Association Research Grant

AD…….....Alzheimer's Dementia

AFNI……...Analysis of Functional NeuroImages

BOLD…….....Blood Oxygen Level Dependent

BPN……Brain Plasticity and Neuroimaging

BU ..... Boston University

CSA……...Chronic Stress and Aging

dACC…….....Dorsal Anterior Cingulate Cortex

DG…….…..Dentate Gyrus

EOD…….Experiences of Discrimination Scale

FDR……..…False Discovery Rate

fMRI…….Functional Magnetic Resonance Imaging

HIV……....Human Immunodeficiency Virus

HOPE……... Health Outreach Program for the Elderly

IQR……..Interquartile Range

MCI……....Mild Cognitive Impairment

MNI…….....Montreal Neurological Institute

MRI……...……...…. Magnetic Resonance Imaging

NDRI……..…..Norepinephrine-Dopamine Reuptake Inhibitor

OEF……...Oxygen Extraction Fraction

PI…….…Principal Investigator

PTSD……...……...…. Post-Traumatic Stress Disorder

ROI…….....Region of Interest

RSN……..…. Resting State Network

SCA……...Seed-based Correlation Analysis

SEM…….....Structural Equation Modeling

SN……..Salience Network

SSRI…….....Selective Serotonin Reuptake Inhibitor

US…….United States

INTRODUCTION

1.1 The Alzheimer's Disease Health Disparity

In 2019, 5.8 million Americans were living with Alzheimer's dementia (AD) (Alzheimer's Association, 2019). In the next 30 years, the prevalence of AD in the aging population in the United States (US) is expected to double (Hebert, Beckett, Scherr, & Evans, 2001). Notably, a larger percentage of the African American and Hispanic population in the US is currently living with AD, when compared to the percentage of White Non-Hispanic Americans living with AD (Chin, Negash, & Hamilton, 2011; Dilworth-Anderson et al., 2008). Due to the prevalence of AD in minority populations and the aging US population, it is important to elucidate the differential underlying biological, cognitive, and social processes involved in the progression of AD. Understanding the disease processes involved in AD can allow us to develop treatments and policies that can delay its onset. If a treatment that delays the onset of AD by 5 years becomes available before the year 2025, the number of Americans living with the disease is projected to decrease by about 30% (*Changing the Trajectory of Alzheimer's Disease: How a Treatment by 2025 Saves Lives and Dollars*, n.d.).

Although extensive research on the disease processes and treatment options for AD has been conducted on non-Hispanic white populations, there are limited investigations regarding AD etiology and treatment in non-white populations (Carmichael & Newton, 2019; Olin, Dagerman, Fox, Bowers, & Schneider, 2002). The limited existing research has demonstrated that African Americans are more than twice as

likely as non-Hispanic whites to have AD and have a lower level of cognitive test performance earlier in the disease's progression (Tang et al., 2001; Weuve et al., 2018). Consequently, further research must be conducted to understand the factors underlying this increased incidence of AD in African Americans, as well as this rapid cognitive decline.

1.2 Biopsychosocial Model of Alzheimer's Disease

There is a broad spectrum of biopsychosocial factors contributing to the progression of AD. Among the biological factors lies a major genetic risk factor, the Apo-E epsilon 4 allele, which is represented among multiple ethnic groups (Farrer et al., 1997). The presence of this allele has been demonstrated to positively correlate with impaired cognitive processes and abnormal hyperactivation of brain regions associated with long-term memory, such as the dentate gyrus (DG), CA3, and CA1 regions of the hippocampus (Sinha et al., 2018).

Research has demonstrated the existence of psychological risk factors for AD, including depression, mental inactivity, and cynicism (Gatchel et al., 2019; Neuvonen et al., 2014; Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008; Wilson et al., 2002). Importantly, the presence of depressive symptoms is common prior to the onset of mild cognitive impairment (MCI) (Gatchel et al., 2019). MCI precedes the onset of dementia, and includes early pathological brain changes such as formation of beta-amyloid plaques, hippocampal atrophy, and decreased vascularity, as well as early symptoms of increased forgetfulness, irritability, or anxiety (Forrester, Gallo, Smith, Leoutsakos, & Forrester,

2016; Jansen et al., 2015; Lopez et al., 2014; Petersen et al., 2001). The early presentation of depressive symptoms prior to both MCI and dementia is important to understanding the etiology of AD through a psychological perspective, but also provides grounds for investigating the social component of depressive symptoms as a possible risk factor for AD. Stress is a predisposing factor for depression, and prior studies have demonstrated a relationship between acute and chronic psychosocial stress and memory decline in older adults, as well as a reversal of hippocampal degeneration upon a decrease in cortisol (Colodro-Conde et al., 2018; Hidalgo, Almela, Villada, & Salvador, 2014; Peavy et al., 2010; Starkman et al., 1999). Consequently, research must be expanded to identify the effects of chronic social stress as a possible risk factor for AD.

In addition to the biological and psychological risk factors for AD, it is important to consider social factors as contributors to the disease's progression. Contextual factors, such as socioeconomic status, education, medical access, and discrimination link race and ethnicity to decreased medical access, decreased physical health and poor health behaviors that ultimately affect cognitive function (Glymour & Manly, 2008).

Additionally, early investigations have recognized a relationship between a lack of social integration and physical and mental health (Berkman, Glass, Brissette, & Seeman, 2000). Social exclusion, measured in subjects by observing their response to a virtual ball-tossing game where they are purposely excluded from the game, has demonstrated a relationship with poor cognitive performance, decreased impulse control, decreased working memory, and increased levels of social anxiety disorder (Baumeister, Twenge, & Nuss, 2002; Heeren et al., 2017; M. Xu et al., 2016, 2018). One recent fMRI

study that used this same virtual ball-tossing game to place subjects in a scenario where they were socially excluded by members of another racial group found that increases in racial discrimination exposure were associated with strong functional connectivity between the amygdala and the anterior insula, in addition to other regions involved in psychosocial function (Clark, Miller, & Hegde, 2018). These cognitive and fMRI studies highlight the impact of social exclusion on cognition and functional brain networks and suggest that social discrimination may be related to altered brain networks.

1.3 Perceived Discrimination as a Salient Stimulus in Emotional Processing

Discrimination is an act of social exclusion that involves "the differential, and often unequal, treatment of people who have been either formally or informally grouped into a particular class of persons." (Law, 2007). Self-reported experiences of perceived discrimination are associated with poor episodic memory, which is implicated in early stages of AD when neurofibrillary changes occur in the medial temporal lobe, the brain region associated with episodic memory (Barnes et al., 2012; Braak & Braak, 1991; De Toledo-Morrell, Goncharova, Dickerson, Wilson, & Bennett, 2006; Jack et al., 1997). In addition to cognitive changes, perceived discrimination is also associated increased depressive symptoms, hypertension, and increased chronic pain (Cozier et al., 2006; Paradies, 2006; Ward, Mengesha, & Issa, 2014). Importantly, these outcome measures just described are not only influenced by perceived discrimination due to race, but also due to discrimination based on gender, disability, age, LGBTQ status, and body weight

(Lyons et al., 2018; Sutin, Stephan, Robinson, Daly, & Terracciano, 2019; Yarns, Abrams, Meeks, & Sewell, 2016).

Discrimination is a considerable salient stimulus to a person experiencing it. A salient stimulus is noticeable, demands attention, and places a load on brain regions that are associated with the processing of emotional stimuli. Consequently, those in social groups who do not frequently experience discrimination are unlikely to find an overt act of discrimination to be a salient stimulus, as it may be relatively undetectable. Furthermore, it is important to note that discrimination may be an act of social exclusion or a covert act of social exclusion, and both contribute to the effects of perceived discrimination and are both considered salient stimuli. For instance, a covert act of discrimination can include a black client consistently noticing they receive poorer service at a restaurant than white clients. Although the act may be subtle, the victim notices a consistent pattern of discrimination and is more likely to identify this event, therefore deeming it a salient stimulus.

1.4 Resting State Functional Network Connectivity and the Salience Network

Recent research in neuroscience has investigated neural activity of large-scale networks across the brain and the implications of such activity on cognition and mood. Human functional magnetic resonance imaging (fMRI) studies observing the fluctuations in the blood oxygen level-dependent (BOLD) signal have demonstrated evidence of the existence of neural activity consistent across various brain regions in the absence of an external stimulus (Raichle, 2015). An increase in activity indicated by BOLD signal

stems from a decrease in oxygen extraction fraction (OEF), or a decrease in the ratio of oxygen consumed to oxygen delivered in brain tissue (Raichle et al., 2001). In other words, when local blood flow increases more than oxygen consumption, the OEF decreases, indicating increased neural activity. Consistent patterns of neural activity have been identified across distant brain regions in the absence task performance, and these functional networks are known as resting state networks (RSNs). Although network nodes may be anatomically distant, the temporal correlations in the BOLD signal suggest that they are functionally connected, forming an RSN.

A number of distinct RSNs have been identified using functional connectivity analysis of fMRI data, including the default mode network, which decreases in activity during specific cognitively demanding goal-oriented behavior (Raichle et al., 2001). This deactivation pattern of the default mode network contributes to the evidence behind the existence of neural networks that are active in the resting state.

One RSN known as the salience network (SN) has been identified across various fMRI studies observing the resting state BOLD signal fluctuations (Menon, 2015). The brain regions comprising the SN, including the dorsal anterior cingulate cortex (dACC) and the orbitofrontal insula, are involved in the processing of salient stimuli, or stimuli that are noticeable and attract attention (Seeley et al., 2007). These stimuli can range from low-level stimuli, such as colors or sounds, or higher-level stimuli involving affective processes, such as an unexpected or surprising stimulus or an emotionally salient stimulus, such as social discrimination (Uddin, 2017). Other structures exhibiting functional connectivity with the SN are the amygdala, ventral striatum, and the substantia

nigra/ventral tegmental area, all of which are involved in the processing of emotions and reward (Cardinal, Parkinson, Hall, & Everitt, 2002; Ilango et al., 2014; Phelps & LeDoux, 2005).

Importantly, SN abnormalities have been associated with memory, mood, and anxiety disorders. Abnormal functional connectivity within the SN and between the SN and other RSNs has been identified in older adults with AD and MCI (Chen et al., 2019; He et al., 2014). Specifically, Alzheimer's patients have demonstrated increased resting-state functional connectivity in the SN (Balthazar et al., 2014). Furthermore, depression, a mood disorder commonly manifesting through repetitive and negative thinking and increased attention to negative stimuli, has been associated with a heightened response in the SN, along with an effect in all of its primary subcortical nodes (Hamilton, Chen, & Gotlib, 2013). Additionally, fMRI studies have demonstrated increased amygdala and insula reactivity during processing of negative emotional stimuli in subjects with anxiety disorders and post-traumatic stress disorder (PTSD) (Stein, Simmons, Feinstein, & Paulus, 2007). Importantly, decreased functional coupling of the insula within the salience network has been demonstrated in subjects with social anxiety disorder when compared to healthy subjects (Liao et al., 2010).

Due to the SN's involvement in emotional processing and various psychiatric and neurological disorders, this RSN is an ideal candidate to study the effects of social discrimination, a highly emotional process, on the underlying functional connectivity of the human brain. The relationship between social discrimination and functional connectivity has been investigated in other brain regions involved in emotional

processing, including the amygdala, but there remains a gap in the literature investigating social discrimination and RSNs involving other brain regions (Clark et al., 2018). As social exclusion has been associated with late-life dementia, decreased long-term memory consolidation, and mood disorders in the elderly, it is important to study the SN in this population (Choi, 2015). There is also limited research on the interaction between the individual SN nodes, the bilateral insula and dACC, and how they individually contribute to the SN as a whole (Han, Eaton, & Marois, 2019; Menon, 2015). As these regions are involved in emotional processing, functional connectivity within the SN may be modulated by social discrimination (Cahill, Babinsky, Markowitsch, & Mc Gaugh, 1995; Davis & Whalen, 2001; Etkin, Egner, & Kalisch, 2011).

Additionally, we will be able to understand the differences in the functional connectivity between SN nodes in black participants compared to white participants. There is an anticipated difference in functional connectivity between black and white participants because black participants will likely endorse more experiences of discrimination than white participants. Therefore, in addition to investigating the relationship between discrimination and functional connectivity of the SN among the black and white participants separately, we will examine the differences between the functional connectivity of the SN between the black and white participants.

1.5 Investigating Functional Connectivity

In recent years, there has been a noticeable increase in research addressing the connectivity of brain regions, which has moved brain mapping research away from

viewing brain regions as functionally segregated and towards viewing brain regions as functionally integrated (K. J. Friston, 2011).

It is important to emphasize the difference between various terms commonly used in neuroscience literature to express neural connectivity in 4-D fMRI datasets: structural connectivity, functional connectivity, and effective connectivity. Structural connectivity refers to the connectivity of network nodes through white matter tracts, measured by diffusion imaging techniques (Sporns, 2007). Functional connectivity corresponds to lack of statistical independence between the activity of neuronal units, indirectly measured with fMRI, that are widespread and often anatomically distant (Sporns, 2007). Effective connectivity refers to the directional effects of one neural population or network node over another, allowing causal effects to be inferred through time series analysis (Sporns, 2007).

In this study, a functional connectivity analysis will be used to investigate the relationship between discrimination and SN functional connectivity. Functional connectivity allows us to quantify connectivity as observed statistical dependencies between regions, in our case by finding a predominant pattern of correlations between neural regions through a method known as seed-based correlation analysis (K. J. Friston, 2011).

Seed-based correlation analysis (SCA) was the first method used to identify the presence of resting state networks by using a hypothesis-driven selection of a region to extract time series data and correlate this data with that of other regions to form functional connectivity maps of covariance with the seed region (Biswal, Zerrin Yetkin,

Haughton, & Hyde, 1995; Cole, Smith, & Beckmann, 2010). This method provides an effective way of identifying the brain regions, clusters of voxels, or individual voxels most functionally connected with the seed region, which will correspond to each primary node of the SN in this analysis (Cole et al., 2010).

1.6 Specific Aims and Hypotheses

In order to investigate the effects of perceived discrimination on the functional connectivity of the multiple nodes of the SN of older adults in the resting state, we will test the following three hypotheses:

1) Hypothesis: Black participants will report more instances of perceived overall and racial discrimination than white participants.

   Aim: Identify the differences in the frequency of perceived overall and racial discrimination between black and white participants.

2) Hypothesis: Each seed region of the SN will demonstrate a significant positive correlation in activity with other SN network nodes among all participants.

   Aim: Identify which seed regions of the SN demonstrate significant positive or negative correlation in activity with other SN network nodes among all participants combined.

3) Hypothesis: Each seed region of the SN will demonstrate a significantly higher positive correlation in activity with other SN network nodes in black participants compared to white participants.

   Aim: Identify which seed regions of the SN demonstrate significantly higher or lower correlation in activity with other SN network nodes that are significantly different between black and white participants.

4) Hypothesis: Greater overall and racial perceived discrimination will predict higher correlation between SN nodes in black and white subjects.

Aim: Identify the effects of perceived discrimination on the correlation in activity between SN nodes for the black and white participants separately.

METHODS

2.1 Participants

The participants for our study were recruited from two sources: The Health Outreach Program for the Elderly (HOPE) study registry at the Boston University Alzheimer's Disease Center, funded by the National Institute on Aging, and participants recruited by our lab for the Chronic Stress and Aging (CSA) Study, funded by an Alzheimer's Association Research Grant (AARG). We used existing neuroimaging and cognitive data from HOPE study participants, all of whom were cognitively healthy white older adults living in the Greater Boston area, in conjunction with psychosocial stress data collected by members of the Brain Plasticity and Neuroimaging (BPN) Lab through the cross-sectional CSA pilot study. The BPN Lab also collected neuroimaging, cognitive, and psychosocial data from cognitively healthy African American adult participants living in the Greater Boston area through the CSA study. In total, 49 native English-speaking older adults were recruited and screened thoroughly for any neurological impairments, visual impairments, psychiatric impairments, cerebrovascular impairments, psychoactive or cardioactive medication use, or claustrophobia prior to being invited to complete study visits. For all participants, we computed the mean age, years of education, subjective social status and percentage of female participants, reported in Table 1.

2.1.1 HOPE Study Participants

The participants recruited from the HOPE study registry included a total of 27 cognitively healthy, non-smoking adults between the ages of 50 and 80 years living in the Greater Boston area for at least the last 40 years. Two participants were excluded from the study due to long-term use of norepinephrine-dopamine reuptake inhibitor (NDRI) and selective serotonin reuptake inhibitor (SSRI) medications, both which demonstrate effects on negative emotion processing and functional neural network connectivity (Anand et al., 2005; Robertson et al., 2007; Rzepa, Dean, & McCabe, 2017; Victor, Furey, Fromm, Öhman, & Drevets, 2013). One participant was excluded from the study due to long-term use of prednisone, a glucocorticoid that has been associated with significant changes in mood and neuroanatomy, even in short doses (Brown, Rush, & Mcewen, 1999; Brown et al., 2004). Nine participants were excluded due to use of statins, which have demonstrated effects on cerebral hemodynamics measured by BOLD fMRI signal, which will be further investigated in this analysis (G. Xu et al., 2008).

After exclusion criteria were applied, there were a total of 15 HOPE study participants who underwent MRI testing and a neuropsychological evaluation. Three HOPE study participants were excluded after MRI processing due to excessive head motion. Twelve HOPE study subjects were included in the analysis, and the participant demographics are detailed in Table 1. All of the HOPE participants identified as White, Non-Hispanic.

2.1.2 AARG Study Participants

The participants recruited from the AARG study included a total of 22 cognitively healthy, non-smoking African American adults between the ages of 50 and 80 years old living in the Greater Boston area for the last 40 years. As with the HOPE study participants, 12 study subjects were excluded due to use of statin medications, glucocorticoid medications, SSRI treatment, or NDRI treatment. Four participants were excluded due to missing or incomplete fMRI data, and 2 participants were excluded after MRI processing due to excessive head motion.

After exclusion criteria were applied, there were a total of 6 AARG study participants who underwent MRI testing and a neuropsychological evaluation. 100% of the participants identified as African-American Non-Hispanic. Participant demographics are detailed in Table 1.

Table 1: Participant Demographics

This table demonstrates the participant demographics across all participants and the demographics within the groups of black participants and white participants. There is a statistically significant difference in years of education between both groups, but no significant difference in gender proportion, subjective social status, community subjective social status, or age.

	All Participants (n=18),	*Black Participants (n=12)*	*White Participants (n=6)*	
Gender (% female), mean(sd)	66.7%	66.7%	66.7%	
Years of Education, mean(sd)	16.5(2.38)	17.58 (1.83)	14.33 (1.86)	p<0.05*
Subjective Social Status, mean(sd)	4.89(1.75)	4.33(1.3)	6(2.1)	p=0.118
Age mean(sd)	70.44 (5.95)	71.2 (4.75)	69(8.20)	p=0.57

Note. HOPE= Health Outreach Program for the Elderly, AARG= Alzheimer's Association Research Grant Study

2.2 Study Visits

Study visits were conducted by research assistants from the Brain Plasticity and Neuroimaging Lab at the Boston University (BU) School of Medicine campus. Prior to evaluation, study staff discussed the study consent form and obtained signed consent from each participant. All study procedures were approved by the BU Medical Campus Institutional Review Board.

For both sets of study participants, we completed a battery of neuropsychological evaluations used to screen participants for cognitive impairments, mood disorders, and to obtain information about general participant demographics. Of note, some of the evaluations collected included the MacArthur Sociodemographic Questionnaire and Experiences of Discrimination (EOD) questionnaire. The MacArthur Sociodemographic Questionnaire provided a subjective measure of socioeconomic status through the subject's perceived standing in the social hierarchy, has been demonstrated to reflect an average of standard markers of socioeconomic status, and is free of psychological biases (Singh-Manoux, Adler, & Marmot, 2003).

In order to measure perceived discrimination, participants were asked to complete the revised version of the EOD, which has demonstrated validity and reliability in evaluating self-reported discrimination across participants in multiple racial and socioeconomic groups (Krieger, Smith, Naishadham, Hartman, & Barbeau, 2005). We focused on a portion of the EOD containing questions related to day-to-day unfair

treatment. This survey consisted of questions regarding the participant's frequency of having experienced an instance of discrimination, such as being "treated with less respect than other people" or "being followed around in a store." The participant was able to report the frequency of the event in their everyday life as "four or more times," "two or three times," "once," or "never." Additionally, subjects were able to attribute the reason for each instance of discrimination to options described on the survey, including race, gender, age, or other reasons.

2.3 MRI Acquisition

All participants underwent MRI testing at the BU School of Medicine Center for Biomedical Imaging. Anatomical and functional MRI scans were obtained using a 3 Tesla Philips Acheiva MRI scanner. The scans collected for each participant included a 3-D T1-weighted turbo field echo (3D-T1-TFE, P reduction: 1.5, S reduction: 2, TR= 6.8 ms, TE= 3.1 ms , flip angle= 9°, scan acquisition duration: 4 min 24 s, field of view= 25 cm , matrix size= 256 x 254;150 slices, resolution= 0.98 mm x 0.98 mm x 1.20 mm) structural scan. We also collected a 10-minute extended resting state fMRI scan, which consisted of 200 BOLD volumes, obtained with a T2 weighted echo-planar imaging sequence (in-plane acquisition resolution= 3.31x 3.37 mm_2, slice thickness= 3.3125 mm, TR=3000 ms, TE=30 ms, flip angle=80°, field of view= 212 x 198.75 mm_2 , matrix size=64 x 59, slices per volume= 48). During the resting state fMRI scan, participants were instructed to watch a fixation cross on a screen while keeping their eyes open, minimizing motion, and letting their mind wander.

2.4 Data Preprocessing

The extended resting state fMRI data were preprocessed using the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996; Cox & Hyde, 1997; Gold et al., 1998). First, T_1-weighted anatomical and BOLD images were visually inspected to identify the presence of artifacts. Then, each subject's BOLD images were de-spiked to remove signal outliers and replace them with values to fit a smooth signal curve. Next, the BOLD images from each subject were interpolated in time to a common reference volume and all data was shifted to correct for differences in image acquisition between slices. To correct for motion, time points where subject movement was greater than 0.5 mm were censored. Each subject's BOLD scan was then aligned with the subject's T_1-weighted anatomical scan. All images were spatially normalized to the Montreal Neurological Institute (MNI) space. Tissue-based regressors, motion parameters, and bandpass regressors were extracted in order to use in correlations to account for nuisance variables such as motion, scanner drift, and noise. Lastly, each subject's BOLD images were spatially blurred, or smoothed, to decrease noise and add up coherent signals, thereby increasing the signal to noise ratio. Four subjects were excluded due to excessive head motion, leading to a total of 18 subjects after preprocessing steps were completed.

2.5 Identification of the Salience Network Regions of Interest

To identify the seed regions of interest in our subjects, masks created from Yeo et. al's 2011 study of cortical parcellations were used (Thomas Yeo et al., 2011). These

masks were converted to MNI space and fit to match our subjects' functional images. Yeo et al. used the resting state data from 1000 subjects to identify the organization within and between resting state networks and create an atlas using exploratory methods such as Independent Component Analysis and Granger Causality Analysis. They identified 17 functionally coupled regions consistent across subjects, including the ventral attention system, which is an aggregate of the salience network and the cingulo-opercular network (Dosenbach et al., 2007; Seeley et al., 2007). Various studies of the salience network have identified the dACC and bilateral insula as the two primary nodes of the network (Menon, 2015; Seeley et al., 2007; Uddin et al., 2013). Therefore, the cortical parcellations for the left insula, right insula, and right anterior cingulate cortex were used as our seed regions for the analysis. The left cingulate cortex was not identified as a region contributing to the salience or cingulo-opercular network in the Yeo et al. atlas of cortical parcellations, so this area was not included as a seed region for our analyses.

2.6 Statistical Analysis

2.6.1 Behavioral Measures

To identify the group differences in the EOD scale score obtained during the study visits, we first scored the survey according to the methods outlined in Krieger et al. 2005. To score the survey, participants who reported "four or more times" were assigned a value of 5, "two or three times" were assigned a value of 2.5, "once" was assigned a

value of 1, and "never" was assigned a value of 0. All values were then summed across test questions to obtain an overall EOD score.

Furthermore, to obtain EOD scores adjusted for the attributed reason for each event of discrimination, the same system for scoring the frequency of discrimination was used, but questions were only scored if the participant attributed the main reason for the experience to a certain cause. For instance, to obtain an EOD score for racial reasons, the summary score was calculated only across instances of discrimination where the participant attributed the main reason for the experience to be "race" or "shade of skin color," while questions where one of these was not the main reason were given a score of 0. This method was repeated for the main reasons for the experience being race, age, gender, or any other reason and scored accordingly.

Subsequently, group differences in EOD score were analyzed using R (R Development Core Team, 2011; Wickham & Wickham, 2009). The overall dataset was split into two data sets, one consisting of the HOPE, or white, study participants and one consisting of the AARG, or black, study participants. Each data set was then tested for the presence of EOD score outliers. Median and IQR scores were calculated for EOD scores for all reasons, race reasons, age reasons, gender reasons, and other reasons for all subjects combined, as well as the black and white participants separately. A Wilcox test was then performed to evaluate the difference in median EOD scores between the black and white participants.

2.6.2 fMRI Statistical Analysis

To test for group differences in activation across our seed regions, fMRI images were analyzed using AFNI to maintain consistency between the methods of preprocessing and statistical analysis, ultimately reducing errors (Cox, 1996; Gold et al., 1998). The seed-based correlation analysis methods are summarized in Figure 1, where the analysis is separated into the steps of extracting time series data, creating correlation maps, and comparing the correlation maps according to the various aims of this study. Each time-series vector is defined by the activity of each voxel in a neural region over the period of time of a scan. A voxel is defined as each 3 mm3 volumetric pixel that comprises a whole fMRI image. When each voxel is concatenated to form a matrix, it now represents that scanned brain region during the total time of the scan.

First, fMRI masks for our seed regions of interest were obtained from the FreeSurfer Wiki website, developed by the Laboratory of Computational Neuroimaging at the Athinoula A. Martinos Center for Biomedical Imaging in collaboration with Yeo et al. ("CorticalParcellation - Free Surfer Wiki," n.d.; Thomas Yeo et al., 2011). These masks were resampled to fit the preprocessed functional data set to ensure coregistration. Both the masks and the functional images were sampled to the Talairach Daemon atlas in standardized Talairach space (Lancaster et al., 2000). Afterwards, the masks were laid over the functional images and the average time series was extracted from each voxel in each seed region for each subject separately. This information was then used to generate subject-specific correlation maps of voxels in the salience network regions of interest (ROIs) that demonstrated positive or negative correlation to the rest of the voxels within

the seed regions. All correlation maps were then converted into Z-score maps to enable comparisons.

Afterwards, a one-sample t-test was performed on the Z score correlation maps to identify which seed regions demonstrated significantly higher or lower activity in comparison to other seed regions among all the participants. Following this, an unpaired t-test was performed on the Z score correlation maps to identify which regions showed significantly higher or lower activity in comparison to the seed region and were significantly different between the black and white participants. Lastly, Spearman correlations were performed for the black subjects' EOD scores for all reasons and Z score maps for each seed region, black subjects' EOD scores for race reasons and Z score maps for each seed region, and white subjects' EOD scores for all reasons and Z score maps for each seed region. Spearman correlations were not performed for white subjects' EOD scores for race reasons as no white participant reported perceived discrimination due to race. These Spearman correlations were performed to identify the effects of EOD scores on the correlation between seed region activity in black vs white participants separately.

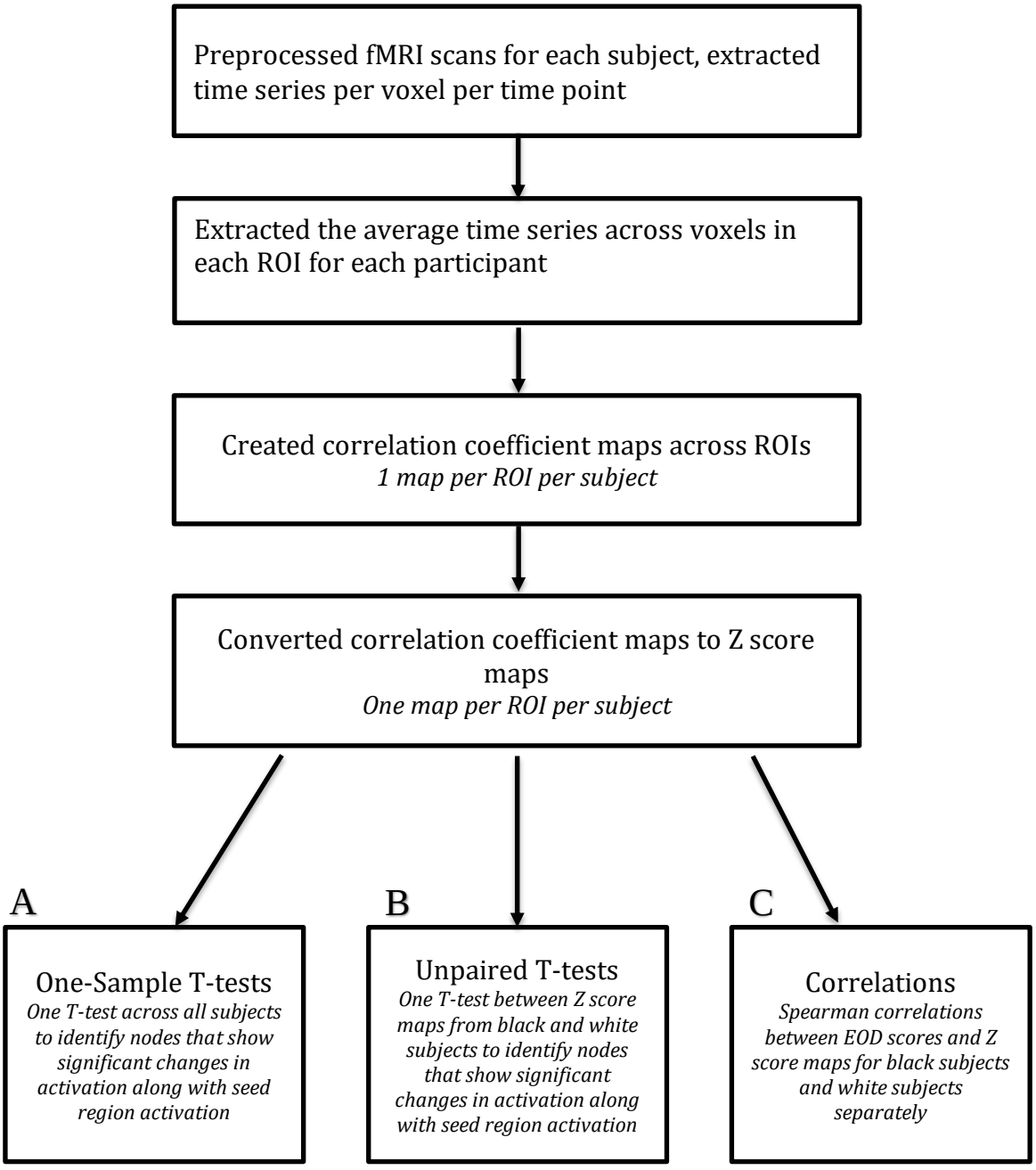

Figure 1: Steps involved in the resting state seed-based correlation analysis of the salience network's functional connectivity

A. Functional connectivity of the salience network regions of interest (ROI) across all participants. B. Differences in functional connectivity of the salience network ROIs between the black and white participants. C. Correlation between perceived discrimination measured by EOD scores with the functional connectivity in black participants and white participants.

RESULTS

3.1 Participant Demographics

To investigate the differences in participant demographics, t-tests were performed between the mean years of education, mean MacArthur Sociodemographic Questionnaire score, and mean age of black and white participants (Table 1). These tests demonstrated that white participants reported significantly more years of education. However, there was no significant difference in subjective social status between black and white participants. There was also no significant difference in the age of black and white participants.

3.2 Group Differences in Experiences of Discrimination

To investigate the differences between the median EOD score between the black and white participants, a Mann-Whitney U-test was performed, reported in Table 2. This test demonstrated that mean EOD scores for all reasons were significantly greater for the black participants (Mdn=21) than the white participants (Mdn=8) ($U=59.5$, $p=0.031$). It also demonstrated evidence that mean EOD scores for race reasons were significantly greater for the black participants (Mdn=19) than the white participants (Mdn=0) ($W=72$, $p=7.49e-5$). There were no significant differences between median EOD scores for age, gender, or other reasons between both groups: (age: $W=33.5$, $p=0.797$; gender: $W=28.5$, $p=0.456$; other: $W=17.5$, $p=0.0642$). Results are detailed in Table 2.

Table 2: Behavioral Measures

Median and Interquartile range (IQR), (1st quartile-3rd quartile) for Everyday Discrimination Scale scores for all participants, black participants, and white participants. A Mann-Whitney U test was performed to evaluate if there was a significant difference in median EOD scores between black and white participants. EOD was reported for all reasons, race reasons, age reasons, gender reasons, or other reasons.

	All Participants	*Black Participants*	*White Participants*
EOD-All Reasons-median (IQR)	10 (7.5-23)	21 (16.75-36.12)	8 (2.375-12.125)
EOD-Race-median (IQR)	0 (0-13)	19 (14.38-35.62)	0 (0-0)
EOD-Age-median (IQR)	0 (0-0)	0 (0-0)	0 (0-0.25)
EOD-Gender-median (IQR)	0 (0-2.5)	0 (0-1.5)	0 (0-5.625)
EOD-Other -median (IQR)	0 (0-4.625)	0 (0-0)	3 (0-8.125)

Note. EOD= Experiences of Discrimination Scale

3.2 Activation across the Regions of the Salience Network in All Subjects

To identify which seed regions of the salience network demonstrated significant positive or negative correlation in activity with clusters in other seed regions of the salience network among all participants combined, we performed a total of three one-sample t-tests. Within each t-test map generated, AFNI's "3dclust" function was used to identify all clusters of voxels sized four voxels or greater, where all positively and negatively thresholded voxels were clustered separately, the faces, edges, or corners of the voxels must touch, and all voxels demonstrated a q-value threshold of $q<0.05$ (Cox,

1996). Q-values, or p-values corrected for multiple comparisons, were used to evaluate significance; this will be further detailed in the discussion. For each cluster, we identified its size, center of mass, Talairach coordinates, and Z-score at the center of mass. Using the Talairach coordinates, the anatomical location of the center of mass was determined in reference to the Talairach Daemon atlas (Lancaster et al., 2000). It was hypothesized that all seed regions of the salience network would demonstrate a significant positive correlation in activity with clusters in other seed regions of the salience network among all participants.

When the left insula was used as the seed region, two clusters survived the clustering analysis. The first cluster that demonstrated significantly higher Z scores compared to a baseline activity of zero among all subjects had a size of 164 voxels and was located at the left insula ($M=0.59$, $SEM=0.01$, $t(17)=10.42$, $q<0.05$). The second cluster that demonstrated significantly higher Z scores compared to a baseline activity of zero among all subjects had a size of 151 voxels and was located at the right insula ($M=0.38$, $SEM= 0.006$, $t(17)=6.905$, $q<0.05$).

When the right insula was used as the seed region, two clusters survived the clustering analysis. The first cluster that demonstrated significantly higher Z scores compared to a baseline activity of zero among all subjects had a size of 164 voxels and was located at the left insula ($M=0.39$, $SEM=0.006$, $t(17)=6.950$, $q<0.05$). The second cluster that demonstrated significantly higher Z scores compared to a baseline activity of

zero among all subjects had a size of 151 voxels and was located at the right insula ($M=0.59$, $SEM= 0.010$, $t(17)=14.73$, $q<0.05$).

When the right anterior cingulate cortex was used as the seed region, one cluster survived the clustering analysis. This cluster demonstrated significantly higher Z scores compared to a baseline activity of zero among all subjects had a size of four voxels and was located at the right anterior cingulate cortex ($M=1.47$, $SEM=0.152$, $t(17)=12.99$, $q<0.05$).

3.3 Differences in Seed Region Correlation Maps Between Black and White Participants

To identify which seed regions demonstrated significantly higher or lower correlation in activity with clusters in other seed regions that were significantly different between the black versus white participants, we performed three unpaired t-tests on the Z-score maps of each participant, one t-test for each seed region. Within each t-test map generated, AFNI's "3dclust" function was used to identify all clusters of voxels sized four voxels or greater, where all positively and negatively thresholded voxels were clustered separately, the faces, edges, or corners of the voxels must touch, and all voxels demonstrated a p-value threshold of $p<0.05$ (Cox, 1996). Q values were not used as in the prior analysis as these results did not survive comparison for multiple corrections. For each cluster, we identified its size, center of mass, location coordinates, anatomical location, Z score at the center of mass, detailed in Table 3. These analyses tested the hypothesis that all seed regions of the salience network will demonstrate a significantly higher positive correlation in activity with clusters in other seed regions of the salience

network in the black participants compared to the white participants given the greater EOD scores of black participants.

First, an unpaired t-test was performed between the black and the white study participants to identify the clusters of voxels in the ROIs that demonstrated a statistically significant difference between both groups. After applying the cluster-extent threshold of four voxels, one six-voxel cluster was located in the right insula that demonstrated a significantly higher correlation with the activation in the left insula in the black subjects when compared to the white subjects, ($M=0.29$, $SEM= 0.03$, $t(17)=2.74$, $p<0.05$). Another four-voxel cluster was also located in the right insula that demonstrated a significantly higher correlation with the activation in the left insula in the black subjects when compared to the white subjects ($M=0.36$, $SEM=0.011$, $t(17)=3.10$, $p<0.05$)

No clusters demonstrated a significantly higher or lower correlation with the activation in the right insula in the black subjects when compared to the white subjects.

One 20-voxel cluster was located in the right insula that demonstrated a significantly lower correlation with the activation in the right anterior cingulate cortex in the black subjects when compared to the white subjects ($M=-0.25$, $SEM=0.0096$, $t(17)= -2.27$, $p<0.05$).

Table 3: Results of unpaired T-test comparing salience network Z-maps of black vs white participants

Cluster Size, Center of Mass anatomical location, mean Z-score between seed region and cluster region at center of mass for black subjects, mean Z-score between seed region and cluster region at center of mass for white subjects, T-value for unpaired t-test comparing black minus white participants. P value threshold of $p<0.05$ and uncorrected for False Discovery Rate, with a minimum cluster size of four voxels.

Seed Region	*Cluster Size*	*Anatomical Location of Cluster*	*Mean Z-Score at Center of Mass- Black Subjects*	*Mean Z-Score at Center of Mass- White Subjects*	*T-value at Cluster Center of Mass*
Left Insula	6	Right Insula	0.30	0.38	2.74
	4	Right Insula	0.51	0.20	3.10
Right Insula	-	-	-	-	-
Right Anterior Cingulate Cortex	20	Right Insula	0	0.10	-2.27

3.4 Relationship Between Perceived Discrimination and Functional Connectivity

For the purposes of this analysis, the black and white participants were separated into two datasets. As described in Table 1, there was a significant difference in the EOD scores for all reasons and for race reasons between the black and white participants, with the black participants reporting greater EOD scores for all reasons and race reasons than the white participants (EOD all reasons- W=59.5, p=0.031; EOD race reasons- W=72, p=7.5e-5) EOD scores are rank scores that do not follow a normal distribution, requiring non-parametric statistics. For this reason, we will consider the black and white

participants separately. To identify the effects of perceived discrimination, demonstrated by the EOD scores for all reasons or race reasons, on the correlation in activity between seed regions for the black and white participants separately, Spearman correlations were performed between the subjects' Z-score maps and respective EOD scores. These analyses tested the hypothesis that higher EOD scores for all reasons and for racial reasons will predict higher correlation between seed regions in the black subjects, but will not predict a higher correlation between seed regions in the white subjects.

3.4.1 Relationship Between EOD Scores and Seed Region Correlation Maps in Black Participants

A Spearman correlation was performed across all black subjects' Z-score maps and the EOD scores for all reasons and race reasons . Results of the Spearman correlation, uncorrected for multiple comparisons, were then viewed using AFNI's "3dclust" function. This was used to identify all clusters of voxels sized four voxels or greater, where all positively and negatively thresholded voxels were clustered separately, the faces, edges, or corners of the voxels must touch, and all voxels demonstrated either an uncorrected p-value threshold of $p<0.05$ or an uncorrected p-value threshold of $p<0.01$ (Cox, 1996). None of the clusters in this analysis survived correction for multiple comparisons due to a low number of subjects, therefore q values were not used and p values were used instead for these preliminary analyses.

Preliminary results of the Spearman correlation indicated there was a strong positive association of the coactivation of the left insula and two clusters and EOD scores

for all reasons, detailed in Table 4. Results also indicated a strong positive association of the activation of the coactivation of the right insula and one cluster and EOD scores for all reasons, detailed in Table 4. Lastly, results indicated a strong negative association of the coactivation of the right anterior cingulate cortex with one cluster and EOD scores for all reasons, detailed in Table 4.

Table 4: Correlations between seed regions and salience network nodes with EOD scores for all reasons among black participants

Cluster Size, Center of Mass anatomical location, Spearman correlation coefficient between seed region correlation map Z score and EOD score for all reasons. P value threshold of $p<0.05$ and uncorrected for False Discovery Rate, with a minimum cluster size of four voxels.

Df= 17.

Seed Region	*Cluster Size (number of voxels)*	*Anatomical Region*	*Spearman Coefficient (rs)*	*p*
Left Insula	8	Right Insula	0.83	<0.05
	6	Left Insula	0.89	<0.05
Right Insula	9	Left Insula	0.83	<0.05
Right Anterior Cingulate Cortex	11	Left Insula	-0.89	<0.05

Note: EOD=Experiences of Discrimination Scale

The preliminary results of the Spearman correlation indicated there was a strongly positive association between coactivation of the left insula with two clusters and EOD scores for racial reasons, detailed in Table 5. Results also indicated a strongly positive association between coactivation of the right insula with one cluster and EOD scores for racial reasons, detailed in Table 5. Lastly, there was no significant association between

coactivation of the right anterior cingulate cortex with any cluster and EOD scores for race reasons.

Table 5: Correlations between seed regions and salience network nodes with EOD scores for race reasons among black participants

Cluster Size, Center of Mass anatomical location, Spearman correlation coefficient between seed region correlation map Z score and EOD score for race reasons. P value threshold of $p<0.05$ and uncorrected for False Discovery Rate, with a minimum cluster size of four voxels.

Df=17

Seed Region	*Cluster Size (number of voxels)*	*Anatomical Region*	*Spearman Coefficient (rs)*	*p*
Left Insula	5	Left Insula	0.94	<0.05
	4	Right Insula	0.89	<0.05
Right Insula	5	Left Insula	0.94	<0.05
Right Anterior Cingulate Cortex	19	Left Insula	-0.77	=0.73

Note: EOD=Experiences of Discrimination Scale

3.4.2 Relationship Between EOD Scores and Seed Region Correlation Maps in White Participants

A Spearman correlation was performed across all White subjects' Z-score maps and the EOD score for all reasons. Spearman correlations were not performed for the EOD score for race reasons as all white participants obtained a score of zero for the EOD for race reasons. Results of the Spearman correlation, uncorrected for multiple comparisons, were then viewed using AFNI's "3dclust" function using the same methods

as the black participants (Cox, 1996). None of the clusters in this analysis survived correction for multiple comparisons due to the low number of subjects, therefore q values were not used and p values were used instead for this preliminary analysis.

Preliminary results of the Spearman correlation indicated there was a moderately negative to strong negative association of the coactivation of left insula with two clusters and EOD scores for all reasons, detailed in Table 6. Results also indicated there was a moderately negative to strongly negative association of the right insula with two clusters and EOD scores for all reasons, also detailed in Table 6. Lastly, there was no significant association between the coactivation of the right anterior cingulate cortex with any cluster and EOD score for all reasons.

Table 6: Correlations between seed regions and salience network nodes with EOD scores for all reasons among white participants

Cluster Size, Center of Mass anatomical location, Spearman correlation coefficient between seed region correlation map Z score and EOD score for all reasons. P value threshold of $p<0.05$ and uncorrected for False Discovery Rate, with a minimum cluster size of four voxels.

Df=17.

Seed Region	*Cluster Size (number of voxels)*	*Anatomical Region*	*Spearman Coefficient (rs)*	*p*
Left Insula	11	Right Insula	-0.59	<0.05
	6	Left Insula	-0.76	<0.05
Right Insula	17	Right Insula	-0.87	<0.05
	4	Left Insula	-0.72	<0.05

Right Anterior Cingulate Cortex	4	Right Insula	0.48	=0.12

Note. EOD= Experiences of Discrimination Scale

DISCUSSION

The goal of this study was to evaluate the differences in the functional connectivity of the various regions of the salience network between black and white participants, as well as the relationship between functional connectivity and perceived discrimination using the EOD. We measured functional connectivity as the correlation between activation in one of the seed regions of the salience network and activation in clusters located in the other seed regions of the salience network. Previous studies have demonstrated abnormalities in resting state activity and functional connectivity of the seed regions of the salience network, such as the insula, in patients with social anxiety disorder and PTSD (Liao et al., 2010; Stein et al., 2007). As we are considering discrimination as a salient stimulus that may also contribute to emotional distress, this suggests that there is a possible relationship between perceived discrimination and functional connectivity of the regions of the salience network.

4.1 Differences in Perceived Discrimination Between Black and White Participants

The results of the Mann-Whitney U test showed that the black participants reported greater perceived overall discrimination than the white participants. It also showed that the black participants reported greater perceived racial discrimination than the white participants. Most discrimination reported by black participants was determined to be for a racial reason, rather than any other social factor or demographic group the participants identified with. However, there was no significant difference in perceived discrimination for gender, age, or other reasons between the black and white participants.

This analysis holds importance because if a larger sample size with greater variation in the self-reporting of the reasons behind the perceived discrimination is used, there is room to evaluate the effect of intersectionality. Intersectionality investigates the relationship between the various social groups that one person may identify with and provides a promising approach towards understanding the effect of discrimination on health outcomes (Bauer & Scheim, 2019; Kapilashrami & Hankivsky, 2018). Although this was not possible in this study, it is important to consider the relationship between race, sex, gender, disability, among other social determinants of health, when investigating discrimination, changes in cognition and neural activity, and health outcomes.

4.2 Functional Connectivity of the Salience Network Across All Participants

The results of the one-sample t-tests performed to identify the functional connectivity between the seed regions of the salience network across all subjects demonstrated significant functional connectivity between the left insula and the right insula, but did not demonstrate significant functional connectivity between the right anterior cingulate cortex and the left or the right insula. These findings survived correction for multiple voxel-wise comparisons using the false discovery rate (FDR) procedure.

These results suggest that across all subjects, all three primary nodes of the salience network were not functionally connected with each other. There was a significant functional connectivity of the left insula with a large cluster of activated

voxels located in the right insula. The size of this cluster, 151 voxels, resembles the size of the right insula as determined by Yeo et al., which was 154 voxels . There was also a significant functional connectivity of the right insula with a large cluster of activated voxels located in the left insula. The size of this cluster, 164 voxels, resembles the size of the left insula as determined by Yeo et al., which was 167 voxels in size. Therefore, the bilateral insula demonstrated significant functional connectivity across all subjects while in the resting state, consistent with previous studies in older adults that also used seed-based correlation analysis (Guo et al., 2012).

However, the right anterior cingulate cortex did not demonstrate significant functional connectivity with either the left or the right insula, so it cannot be concluded that all three primary nodes of the salience network were functionally connected with each other. This is consistent with a recent study conducted that used the "oddball" task, which places the subject in a situation where they are socially excluded, to examine the function of the anterior insula and anterior cingulate cortex separately (Han et al., 2019). They concluded that the insula demonstrated a sustained response to affective events and a transient response to neutral events, whereas the anterior cingulate cortex demonstrated a transient response to all events. If the anterior insula demonstrates a more sustained response than the anterior cingulate cortex, it is likely that the resting state will reveal a greater connectivity between the bilateral insula and will not easily reveal connectivity between the anterior cingulate cortex and the insula. However, the Han et al. study was performed in the presence of a task, and the different contributions of the insula and the anterior cingulate cortex to the salience network in the task-free resting state remain

unclear. Additionally, other studies have demonstrated functional connectivity between the anterior cingulate cortex and the insula in younger subjects, and have also used different methods to measure functional connectivity such as independent component analysis (Seeley et al., 2007; Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2012). It is possible that our older adult subjects and use of seed-based correlation analysis did not allow us to replicate the functional connectivity patterns seen in these previous studies.

4.3 Differences in Functional Connectivity of the Salience Network Between Black and White Participants

The results of the independent t-tests performed in this analysis demonstrated a significantly higher functional connectivity of the left insula and the right insula in black participants compared to white participants, when using the left insula as the seed region to identify functionally connected voxels in other seed regions. No significant differences between the black and white participants were found when using the right insula as a seed region to identify functionally connected clusters of voxels in other seed regions of the salience network. Interestingly, black participants demonstrated decreased functional connectivity between the right anterior cingulate cortex and the right insula compared to the white participants.

The increased functional connectivity between the left and right insula in the black participants of this analysis is consistent with the hypothesized relationship between race and salience network connectivity. The decreased functional connectivity between the right anterior cingulate cortex and right insula among the black participants

may be partially explained by stress-related noradrenergic remodeling of neural networks. One study suggests that connectivity in a network comprising the frontoinsular cortex and the dorsal anterior cingulate cortex increased after exposure to a fear-inducing acute stressor, and this increase was attenuated by blocking beta-adrenergic receptors (Hermans et al., 2011). Interestingly, multiple studies have demonstrated evidence of decreased beta-adrenergic receptor function in black subjects, exacerbated in the context of hypertension and its comorbidities of obesity and overweightness (Jain, Dimsdale, Roesch, & Mills, 2004; Sherwood, Hill, Blumenthal, Johnson, & Hinderliter, 2017). Taken together, this evidence can explain our findings of decreased connectivity between the insula and anterior cingulate cortex in black participants.

Although these preliminary findings suggest a difference in functional connectivity between black and white participants, none of these findings survived FDR correction. This is likely due to a small sample size and high proportion of subjects that were excluded from the study due to excessive head motion or exclusion due to pharmacological treatments the subjects were undergoing, reducing generalizability of these results to the population.

4.4 Relationship Between Perceived Discrimination and Functional Connectivity of the Salience Network in Black Participants

The results of the correlation performed between the functional connectivity of the seed regions of the salience network and EOD scores for all reasons and race reasons suggested a possible relationship between perceived discrimination and altered functional

connectivity within the salience network. However, these preliminary findings did not survive FDR correction, so they may not be generalizable to the population.

Our data suggests that perceived discrimination moderates the functional connectivity between the left and the right insula in the black participants, when using both the left insula and the right insula as the seed region for the analysis. Interestingly, there was a significant negative correlation between the functional connectivity of the right anterior cingulate cortex with the left insula and EOD scores for all reasons within the black participants. This suggests that increasing perceived discrimination has an attenuating effect on the connectivity of the right anterior cingulate cortex with the left insula in the black participants.

Furthermore, the relationship between EOD scores for all reasons and functional connectivity between the left and right insula was maintained when evaluating the correlation between EOD scores for racial reasons alone and functional connectivity between the seed regions of the salience network in the black participants. This demonstrated that increasing perceived racial discrimination has an augmenting effect on the functional connectivity between the left and right insula in black participants. Additionally, there was a strongly positive correlation between the functional connectivity within the left insula and EOD scores for race reasons, demonstrating that increasing perceived racial discrimination has an augmenting effect on the functional connectivity within the left insula in black participants. Lastly, the correlation between the functional connectivity of the right anterior cingulate cortex with the left insula and EOD due to racial reasons did not demonstrate a significant effect of perceived racial

discrimination on the functional connectivity between the right cingulate cortex and the left insula in black participants.

The results of these analyses are consistent with studies that demonstrate increased activity of the anterior insula in response to social pain, or pain caused by social rejection (Eisenberger, Lieberman, & Williams, 2003; Stillman et al., 2010; Way, Taylor, & Eisenberger, 2009). However, our findings of the attenuating effect of perceived discrimination for all reasons on the functional connectivity of the right anterior cingulate cortex with the right insula in the black participants may be explained by findings from a study observing the neural activity involved in social pain and emotional regulation in black participants. This study reported that black participants with high distress exhibited greater social pain-related neural activity in the dACC and the anterior insula in response to a social exclusion task (Masten, Telzer, & Eisenberger, 2011). Interestingly, black participants in the Masten et al. study who attributed social exclusion to racial discrimination demonstrated decreased social pain-related neural activity and increased emotional regulatory neural activity in the prefrontal cortex and rostral anterior cingulate cortex, which is consistent with our findings of the relationship between increased perceived discrimination for all reasons and decreased functional connectivity of the right anterior cingulate cortex with the right insula in black participants. This suggests that our functional connectivity observations may be complicated by the presence of both social pain-related neural activity and emotional regulatory neural activity in the prefrontal cortex and anterior cingulate cortex. Furthermore, it is possible no significant relationship was found between functional

connectivity between anterior cingulate cortex and insula and EOD scores due to race because other emotional regulatory mechanisms that affect social-pain related neural activity were not accounted for in our analyses.

4.5 Relationship Between Perceived Discrimination and Functional Connectivity of the Salience Network in White Participants

Results of the Spearman correlation used to identify the relationship between perceived discrimination and functional connectivity across seed regions of the salience network in white participants demonstrated opposite findings from the results in the black participants. It is important to note that we did not evaluate the relationship between perceived racial discrimination and functional connectivity in the white participants, as no white participant in these analyses reported an instance of perceived discrimination due to a racial reason. However, these preliminary findings did not survive FDR correction, so they may not be generalizable.

The correlation between EOD scores for all reasons and the functional connectivity between the left insula and the right insula demonstrated that increasing EOD scores for all reasons were related with decreased functional connectivity between the left and right insula in the white participants. Furthermore, there was no significant effect of EOD for all reasons on the functional connectivity between the right anterior cingulate cortex and the right insula in the white participants.

The negative correlation between perceived overall discrimination and functional connectivity in the salience network in white participants may be explained by the

presence of emotional mechanisms such as neuroticism. Neuroticism refers to a person's increased susceptibility to experiencing negative emotional states (Larsen & Ketelaar, 1991). Studies have demonstrated that neuroticism moderates the negative correlation between discrimination and cognition, as well as that those who display higher neuroticism report increased instances of memory failures on days where they experience increased stressors (Barnes et al., 2012; Neupert, Mroczek, & Spiro, 2008). Additionally, there is evidence that increased variations in whole-brain resting-state functional connectivity can predict neuroticism, and that highly neurotic people demonstrate decreased functional connectivity in the whole brain, which is consistent with our functional connectivity findings in white older adults (Hsu, Rosenberg, Scheinost, Constable, & Chun, 2018; Servaas et al., 2014). Servaas et al. also suggested that highly neurotic people may have decreased network organization, less clear delineation of functional subnetworks, as well as decreased ties of the cingulo-opercular subnetwork with other functional subnetworks. Interestingly, the cingulo-opercular subnetwork has been aggregated with the salience network to comprise the ventral attention network, which is involved in the re-orienting of attention to salient stimuli (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). Therefore, the inverse relationship between perceived overall discrimination and functional connectivity in this analysis may be explained by neuroticism.

4.6 Limitations

4.6.1 The Multiple Comparisons Problem

It can be argued that the most significant limitation of this study is the inability for most of our significant results to survive correction for multiple comparisons. The multiple comparisons problem is prevalent in functional neuroimaging due to the large quantity of data collected in subject scans resulting in a large number of voxel-wise comparisons, and can be addressed by using correction methods such as the familywise error rate (FWER) or the FDR procedure to minimize Type I errors (Bennett, Wolford, & Miller, 2009).

The results of the first aim, which identified activation across the regions of the salience network for all subjects, did survive correction for multiple comparisons using an FDR-corrected statistical threshold. It is reasonable to infer that the salience network is a resting state network that is robustly identifiable among healthy older adults. However, the rest of the aims did not produce results that survived correction for multiple comparisons using an FDR threshold, therefore they have to be interpreted with caution and may not be generalized to the population and cannot be said to reflect true effects. The primary way to address this in our studies in the future is to increase our sample size.

4.6.2 fMRI Limitations

The BOLD signal has been widely used in fMRI techniques to map neural activity in the brain, using the basis of cerebral blood flow as a marker of brain function (Faro, Haughton, & Mohamed, 2006). However, as the BOLD signal is a measure of cerebral

hemodynamics, there are other physiological contributions to the BOLD signal that change blood flow through the cerebral vasculature, including cardiac hemodynamics and respiration (Kennan, Zhong, & Gore, 1994; Raj, Anderson, & Gore, 2001). These measures can be controlled for in fMRI studies by measuring pulse and respiratory rate while subjects are in the MRI scanner and using those as regressors when performing seed-based correlations, but this was not performed in our study. Additionally, vascular density within regions of interest can also affect the BOLD signal. When neighboring regions exhibit vascular overlap, BOLD signal in one voxel will likely result in a similar signal in neighboring voxels, possibly leading to an inaccuracy in the size of detected activation clusters (Cavaglia et al., 2001). Lastly, it is important to note that the scanner acquisition parameters in this analysis may provide lower statistical power due to the long repetition time of the resting state scan (Faro et al., 2006). Since this limitation is method-specific, converging evidence from other cognitive neuroscience and neuropsychological assessment methods are needed.

4.6.3 Subject Demographic Limitations

Although the subject groups in this study were matched in age, subjective socio-economic status, and gender, it is important to consider how these factors may contribute to the observed BOLD response within participant groups. Studies have demonstrated that variability in the BOLD signal has a strong relation with age and that hemodynamic properties of the cerebral cortex change with age (Huber et al., 2015; Tian et al., 2010; Zhao, Wen, Cross, & Yablonskiy, 2016). Additionally, studies have observed abnormalities in salience network connectivity and structure in normal aging, as well as

in older adults with mild cognitive impairment (Andrews-Hanna et al., 2007; Goldstone et al., 2016; He et al., 2014). Age was not used as a covariate when performing correlations with EOD scores in our study, so it has a potentially confounding effect on the relationship between perceived racism and functional connectivity, however, this is unlikely since the two groups did not differ in age. Subjects were screened out if they demonstrated evidence of mild cognitive impairment, so this would not be a confounder in this case. Furthermore, although the subjects were matched in subjective socioeconomic status, they were not matched in years of education, with white participants reporting significantly more years of education (Table 1). Although subjective socioeconomic status is free of bias and is a marker of socio-economic status, low years of education is a risk factor for cognitive decline and has been more widely studied than subjective socioeconomic status (Singh-Manoux et al., 2003). It is likely that the differences in level of education between the subject groups contributed to the differences observed in the functional connectivity of the SN.

In addition, subject groups were matched in proportion of female and male participants between groups, but there were more females than males in both groups and sex was not considered as a covariate in our analyses. Studies have demonstrated differences in the BOLD response between men and women in task-related study designs, which may correspond to a sex difference in stimulus processing or a sex difference in the underlying physiology of the BOLD signal changes (Gorbet & Sergio, 2007; Levin et al., 1998; Moulton, Keaser, Gullapalli, Maitra, & Greenspan, 2006). However, there is little evidence for differences in the BOLD response in the salience network between

men and women measured at rest, including in older adult participants (Goldstone et al., 2016; Weissman-Fogel, Moayedi, Taylor, Pope, & Davis, 2010).

4.6.4 Salience Network Limitations

The salience network provides a model for investigating the neural processing of behaviorally relevant stimuli, such as instances of perceived discrimination (Menon, 2015). However, the salience network is not an isolated system, but acts in tandem with other readily-identifiable RSNs, such as the default mode network and the central executive network. Studies have demonstrated that the insula, a primary node of the salience network, exerts a causal control over the default mode network and the central executive network when subjects are undergoing task-switching (Chand & Dhamala, 2016; Chiong et al., 2013; Goulden et al., 2014). In the current analyses, the seed regions were limited to the primary nodes of the salience network and we only observed the functional connectivity between the right insula, left insula, and right anterior cingulate cortex (Thomas Yeo et al., 2011). This was done to reduce the size of our data from all the voxels in the brain to only the voxels in those regions, lowering the FDR-corrected statistical threshold. However, this analysis would have benefitted from an exploration of the functional connectivity of the SN primary nodes with other brain regions that provide input to the primary nodes, such as the amygdala, ventral striatum, and ventral tegmental nuclei (Menon, 2015).

In addition, the left anterior cingulate gyrus was not observed as a seed region in this analysis, as it was not identified as a salience network seed region in the atlas of cortical parcellations used to identify the ROIs for this study (Thomas Yeo et al., 2011).

Also, the liberal ROI mask of the seed regions available on the Freesurfer website was used, rather than the tight mask that provides smaller parcellations of the seed regions, which may contribute to inaccurate anatomical localization of activated clusters in regions near the insula.

4.6.5 Limitations of the EOD

The demographic representation of the participants in this study provides a limitation to the EOD, as the EOD is focused towards a working class demographic where there is disproportionate representation of people of color (Krieger et al., 2005). Although our subjects were matched in subjective social status, they were not matched in years of education, according to Table 1. This may present as a potential confounding variable in our interpretation of the EOD, as it is aimed towards working class participants and all of our subjects may not necessarily be considered a part of this group.

Furthermore, this self-report of experiences of discrimination is insufficient to evaluate all the different ways that racism occurs, including internalized racism, institutional/structural racism, or residential segregation (Krieger et al., 2005). The 10 items on the day-to-day unfair treatment portion of the EOD that was used in this study primarily focuses on interpersonal racism, so a more comprehensive self-report or observational study would be necessary to address different types of racism, such as institutional and internal racism. Additionally, this self-report suffers from recall bias that may be due to experiencing the event a long time ago, or consciously or unconsciously forgetting a traumatic experience of racism (Porter & Birt, 2001). An alternative method of measuring perceived discrimination would be to inflict a discriminatory situation on a

subject as was done in previous studies using a virtual ball-tossing game, but this cannot be used to study chronic effects and would only be useful to examine acute effects of discrimination (Baumeister et al., 2002; Heeren et al., 2017; M. Xu et al., 2016, 2018).

4.7 Future Directions

Based on the findings of this analysis, it would be beneficial to increase recruiting efforts to increase the number of subjects, especially the number of black participants. As this is an ongoing study, more participant data will be collected in the future. This would have the benefit of allowing the trends observed in our analyses to survive correction for multiple comparisons due to increased statistical power. In addition to enrolling more subjects, other brain regions linked to the salience network and involved in emotional regulation should be studied in the context of perceived discrimination. Prior research has demonstrated increased levels of spontaneous amygdala activity are associated with greater discrimination exposure as measured by the EOD (Clark et al., 2018). Additionally, there has been evidence of increased changes in the anatomical shape of the amygdala and the hippocampus in association with higher social adversity in human immunodeficiency virus (HIV) positive individuals (Thames et al., 2018). Given these findings, expanding our regions of interest to include other cortical regions involved in emotional processing would be valuable.

Furthermore, this analysis was conducted by investigating the functional connectivity of the regions of interest. Importantly, functional connectivity has been widely used but is merely a statistical descriptor of data, so it makes minimal

assumptions about the underlying physiological mechanisms of neural networks (Seth, Barrett, & Barnett, 2015). Alternatively, investigating effective connectivity allows the elucidation of the simplest possible circuit diagram for a neural network that explains an observed response and allows us to observe directed functional interactions between time series data (K. Friston, Moran, & Seth, 2013). In future studies, methods such as dynamic causal modeling, structural equation modeling, and conditional Granger causality can be used to investigate the effective connectivity between our ROIs (K. J. Friston, 2011).

CONCLUSION

In conclusion, there is support for the hypothesis that black participants demonstrate higher functional connectivity between the primary nodes of the SN compared to white participants and that higher EOD scores for all reasons and racial reasons predict higher functional connectivity in the SN of black participants, but not in white participants. However, these results are preliminary and did not survive correction for multiple comparisons. These preliminary results demonstrated that black participants exhibited greater functional connectivity between the left insula and the right insula compared to the white participants and decreased functional connectivity between the right anterior cingulate cortex and right insula compared to the white participants. Additionally, there was a positive association between the functional connectivity of the left insula with the right insula and perceived discrimination in the black participants, as well as a negative association between the functional connectivity of the right anterior cingulate cortex with the left insula and perceived discrimination in the black participants. Lastly, there was a positive association between the functional connectivity of the left insula with the right insula and perceived racial discrimination in the black subjects. Given the lack of survival for correction for multiple comparisons, further analyses should be conducted on a larger sample of subjects. Additionally, functional connectivity analyses should be conducted on a wider span of neural regions that interact with the salience network and are not limited to the primary nodes of the network. Despite the lack of generalizability of these current findings, there is strong support in other studies for the role of perceived discrimination and other forms of social adversity

on neural changes measured by connectivity, task performance, and neuroanatomical measures. Further research in the field should consider discrimination as a risk factor for aberrant neural changes, and move away from seeing race itself as a risk factor. Additionally, little is known about the interpersonal, social, and societal contributions to the brain functional network changes involved in healthy aging, AD, and the AD health disparity, so further research in this area is necessary.

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