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Predicting Reappraisal Success with Innate Neural Connectivity Across the Adult Lifespan

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A Thesis Presented

by

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ABSTRACT

Predicting Reappraisal Success with Innate Neural Connectivity Across the Adult Lifespan

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Reappraisal — reinterpreting a situation to change emotional response — is an effective emotion regulation strategy that relies on cognitive control network activity, including engagement of the dorsolateral prefrontal cortex (dlPFC), to attenuate amygdala activity. Greater dlPFC-Amygdala functional connectivity predicts instructed reappraisal task success, and daily use of reappraisal for younger adults (Pico-Perez et al.., 2018) but not older adults (Opitz et al., 2012), while the connectivity of the vmPFC is predictive of physiological markers of ER success for all ages (Sakaki et al., 2016 & Urry et al., 2006). However, the relationship between Resting-State Functional Connectivity (RSFC) and reappraisal task success across the lifespan has yet to be investigated. Participants in the Cambridge Center for Aging Neuroscience study (N=299) completed an 8-minute resting-state fMRI scan. In each trial of an emotion regulation task, participants either viewed or reappraised a negative film and reported post-regulation positive affect. RSFC across bilateral amygdala and the mPFC, the left and the right dlPFC were calculated with Matlab's CONN Toolbox. The hypothesis is that the strength of the amygdala-mPFC RSFC will predict lower negative and higher positive affect scores after reappraising, however, this study data failed to find evidence to support this hypothesis. The

association between the amygdala-dlPFC RSFC and post-reappraisal negative affect scores was moderated by age. Positive affect was higher when there was a stronger negative RSFC in young and middle-aged adults, and this relationship was not significant at older ages (~72). Our results suggest that dlPFC-amygdala activity at rest may be a predictor of emotion regulation in younger and midlife adults but that dlPFC-amygdala activity may be less predictive of emotion regulation outcomes in later life.

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CHAPTER 1

INTRODUCTION

Emotion regulation (ER) is crucial to mental health and well-being across the lifespan. Reappraisal is one of the most effective and well-studied strategies of ER (Webb, Miles, & Sheeran, 2012; Parkinson & Totterdell, 1999). Reappraisal involves thinking about an emotional stimulus to change its meaning with the goal of increasing positive affect and/or decreasing negative affect (Gross, 1998; McRae, Ciesielski, & Gross, 2012; Oschner & Gross, 2005). Successful reappraisal is associated with activation of frontal brain regions, which leads to decreased activation of the amygdala (Buhle, 2014; Kanske, 2011; McRae, Ciesielski, & Gross, 2012; Oschner & Gross, 2005). The use of reappraisal as an ER strategy develops during late adolescence and becomes a frequent strategy in early adulthood (McRae et al., 2012, Silvers et al., 2015) and across the life span into old age (John & Gross, 2004). While older adults tend to perform behaviorally as well as - or better than - younger adults in reappraisal tasks (Nowlan, Wuthrich, & Rapee, 2015; Shiota & Levenson, 2009; Yeung, Wong & Lok, 2011), the neural correlates of this success seem to shift. While the lateral prefrontal cortex (lPFC)-amygdala connection is the best predictor for reappraisal success through the majority of the adult age span (Buhle et al., 2014) the medial prefrontal cortex (mPFC) region seems to play a key role in the ER and specifically in the reappraisal success of older adults (Allard & Kensinger 2014; 2014b; Opitz, Rauch, Terry, & Urry, 2012; Urry et al., 2006).

Most ER imaging studies examine either activation or task-based functional connectivity (FC), which is synchronous activity of two or more neural regions during a task. Only a few studies about the neural correlates of reappraisal have used the more accessible measure of resting-state functional connectivity (RSFC). These RSFC studies are informative but limited

because they use proxy variables of emotion regulation - such as self-report or physiological measures – rather than direct behavioral outcomes (Picó-Pérez et al., 2018; & Sakaki et al., 2016). Furthermore, the majority of RSFC studies of reappraisal success have mainly focused on younger to middle-aged adults (Morawetz, et al., 2016; Picó-Pérez et al., 2018; Uchida et al., 2015). While the lPFC-amygdala task-based FC has been the greatest predictor for young to middle-aged adults' reappraisal success (Buhle et al., 2014; Ochsner & Gross, 2005; Ochsner, Bunge, Gross, & Gabrieli, 2002), we do not yet know which regions at rest best predict reappraisal success in older adults. Correlating RSFC measures to reappraisal success in a behavioral task may help to better understand which regions are the primary drivers of reappraisal success across the *entire* lifespan.

This study aims to clarify which neural networks best predict reappraisal success across the lifespan. The use of RSFC may serve as a cost-effective and accessible tool for investigating how older adults maintain emotion regulation ability. Utilizing the Cambridge Center for Aging Neuroscience (Shafto et al., 2014) public data set of adults aged 18-88 (Shafto et al., 2014), we will investigate associations between reappraisal success and two resting-state networks, namely the amygdala to the dlPFC and the amygdala to the mPFC. We predict that the association between the mPFC and amygdala at rest will correlate with reappraisal task success across all ages of the adult lifespan. Reappraisal task success is indicated by either decreased negative affect, or increased positive affect compared to a baseline measure. In contrast, we predict that the association between the dlPFC and amygdala at rest will be moderated by age, such that it will be stronger in younger and middle-aged adults than in older adults.

1. 1 Neural Correlates of Reappraisal

Reappraisal requires attending to a negative stimulus, the experience of an emotion, and cognitive regulation of the emotion (Gross 1998; Oschner & Gross, 2005). Emotion generation starts with activity in the amygdala, which is a neural region associated with affective experience and the salience of emotional stimuli (Adolphs & Tranel 1999; Hamann, Ely, Grafton, & Kilts, 1999). During ER tasks, a decrease in amygdala signal is considered a neural biomarker of reappraisal success (Zhou et al., 2008). Reappraisal activates a well-established inhibitory network of cognitive control regions in the brain (Moodie et al., 2020).

The dlPFC region is one of the most consistently active regions during reappraisal for young to middle-aged adults (Buhle et al., 2014; Dickhof, Falkai, & Gruber, 2011; Frank et al., 2014; Morawetz et al., 2017). The strength of the inverse connection between lPFC regions and the amygdala is predictive of engagement in self-reported reappraisal (Drabant, McRae, Manuck, Hairi, & Gross, 2009; Picó-Pérez et al., 2018) and reappraisal task success (Banks, Eddy, Angstadt, Nathan, & Phan 2007; Kanske, Heissler, Schonfelder, Bongers, & Wessa, 2010; Payer, Baicy, Lieberman, & London, 2012; Sarkheil, Klasen, Schneider, Goebel, & Mathiak; 2019).

Some studies indicate that the mPFC also is involved in cognitive reappraisal (Ochsner, Bunge, Gross, & Gabrieli, 2002; Ochsner & Gross 2005, Opitz, Rauch, Terry, & Urry, 2012). However, a later meta-analysis that incorporated these studies failed to find evidence that the mPFC showed peak activation during instructed reappraisal (Buhle et al., 2014). The mixed findings suggest that the mPFC may be involved in an auxiliary role in reappraisal. The mPFC is engaged during the appraisal of the stimuli and may assign affective meaning to a stimulus (Kober et al, 2008; Roy, Shohamy, & Wager, 2012), as well as cognitive labeling of specific momentary emotional states (Mitchell, 2009). The mPFC is hypothesized to play a role in

self-reflection, which may facilitate emotion identification (Urry & Gross, 2010). One study showed the mPFC was active during a reappraisal task that asked individuals to increase the self-relevance of the displayed image and modulate emotional reactions in response to viewing that image (Morawetz, Bode, Baudewig & Heekeren, 2017). Lesions of mPFC in neurosurgical patients are associated with elevations in amygdala activity in response to negative images, suggesting ineffective emotion regulation (Motzkin, Philipini, Wolf, Baskaya, & Koenigs, 2014). Another group examined which neural regions correlated with an individual's heart rate variability (HRV), in an explicit ER task (Steinfurth et al., 2018). The ventral mPFC was active during reappraisal for a group with high HRV and not for individuals in the low HRV group (Steinfurth et al., 2018). The findings provide evidence that the vmPFC is involved in reappraisal, and can be more active during reappraisal for individuals with greater innate ER ability (the high HRV group). One study demonstrated that the vmPFC served as the main region for relaying the prefrontal control regions to the amygdala, and therefore suggests a recursive feedback loop through which the frontal regions can affect the amygdala and update conscious regulation behavior accordingly (Steward et al., 2021). Thus, while the mPFC may not be consistently active during reappraisal, it might play a role in the self-regulation and appraisal of the success of reappraisal, rather than directly reducing amygdala activity.

1.2 Neural Differences in Reappraisal due to Age

The mPFC is a well-preserved brain region in older adults (Gutchess, Kensinger, & Schacter, 2007), thus potentially making it a more crucial region in reappraisal for older than younger adults. After reappraisal, decreased amygdala activation and lower negative affect ratings of an image are associated with greater activity in the mPFC in older adults, rather than the lPFC as is typically seen in younger and middle-aged adults (Urry et al., 2006). Stronger

negative correlations between the mPFC and the amygdala, rather than the lPFC control regions, also lead to greater cortisol recovery in older adults, suggesting a reliance on medial regions for daily stress management (Urry et al., 2006).

Data from activation and task-based FC studies indicate that involvement of the lPFC in emotion regulation is lesser for older than younger adults (Urry et al., 2006; Opitz, Rauch, Terry, & Urry, 2012). Opitz et al. (2012) found that dlPFC activity was associated with reappraisal success for younger but not older adults. In task-based reappraisal-FC studies, the connectivity between the lPFC and other regions involved in emotion regulation tends to be stronger in younger adults than in older adults (Allard & Kensinger, 2014; Leclerc & Kensinger, 2008). In one task-based FC study of reappraisal, participants were asked to reduce negative feelings after viewing negative film clips. During reappraisal, younger adults demonstrated stronger connectivity between the lPFC and the anterior cingulate cortex (ACC) than older adults (Allard & Kensigner 2014).

There are limited studies of emotion regulation success that utilize RSFC, especially ones that include older adults. Most studies have focused on younger and midlife adults, and found that seed-based RSFC has been shown to be predictive of successful reappraisal use (Picó-Pérez et al., 2018; Uchida et al., 2015) but whole-brain RSFC has not been shown to be predictive of reappraisal use (Burr et al., 2020). One seed-based RSFC study showed that the prefrontal regions were predictive of self-reported reappraisal in young to middle-aged adults (Picó-Pérez et al., 2018). Of the two studies that used seed-based RSFC in older adults, results support the role of the mPFC in emotion regulation success (Sakaki et al., 2016; Urry et al., 2006). Older adults with stronger negative mPFC-amygdala connectivity were able to bring their cortisol levels back within the normal range after a stressor, faster than those with weaker connectivity

(Urry et al., 2006). Further, mPFC-amygdala connectivity was predictive of greater HRV – an indicator of successful emotion regulation - for younger and older adults, while the vlPFC connectivity to the amygdala was only predictive of HRV for younger adults (Sakaki et al., 2016). Thus, for older adults, strong positive mPFC-amygdala connectivity– and not the dlPFC-amygdala connectivity – may be associated with implicit indicators of reappraisal success.

1.3 The Current Study

This study seeks to better understand age differences in the neural circuits that are associated with behavioral measures of successful reappraisal. The current study will determine how age moderates the association between two RSFC networks (i.e., mPFC with the bilateral amygdala, dlPFC with the bilateral amygdala) with negative and positive affect after reappraising a negatively valenced film clip. Based on previous literature (Sakaki et al., 2016; Uchida et al., 2015; Urry et al., 2006), we hypothesize that a strong positive mPFC-amygdala RSFC will be associated with reappraisal success regardless of age. The mPFC is involved in assessing when reappraisal should occur for all ages, the mPFC does not deteriorate physiologically, and the connectivity of this region does not decline in older adults (Gutchess, Kensinger, & Schacter, 2007; Sun et al., 2016). In contrast, we expect the association between dlPFC-amygdala RSFC connectivity and reappraisal success to be moderated by age (Allard & Kensigner 2014; Opitz, Rauch, Terry, & Urry, 2012). The moderation effect will be such that the dlPFC-amygdala RSFC will be a stronger predictor of reappraisal success for younger and midlife adults than for older adults.

CHAPTER TWO

METHOD

2.1 Participants

Participant data were drawn from the Cambridge Center for Aging and Neuroscience (Cam-CAN) study, which was designed to understand how age-related neural changes affected cognitive functioning over the adult lifespan (Shafto et al., 2014). Mandated healthcare service registration records were used to sample the entire Cambridge, U.K. area population, where anyone who was eligible was sent an invitation letter. Exclusion criteria were severe cognitive impairment, communication issues such as hearing loss or insufficient English language, mobility impairments, substance abuse issues or current drug usage, major medical issues (e.g., Parkinson's, Stroke, Cancer), or MRI scanning contraindications (e.g., metallic implants, claustrophobia) (Shafto et al., 2014).

Data from participants who completed the emotion regulation behavioral task, the resting-state fMRI scan, and the structural MRI scan – all of which are described below – were utilized for this study (N = 299; age range 18-88, M = 54.4, SD = 18.6; 50% female).

2.2 Procedures

In the original CamCAN study, the participants went through 3 stages of data collection. Data for the current study came from stage two. At stage two, participants (1) engaged in an MRI scan, which included both structural and resting-state functional imaging, (2) participated in a 55-minute emotion regulation task, and (3) completed a 5-minute cognitive task, the Cattell test of fluid intelligence, as part of a series of behavioral measures.

2.2.1 *fMRI Acquisition*

The neuroimaging data were gathered during a one-hour session conducted on a 3T

Siemens TIM Trio System, using a 32-channel head coil. The MRI session included a pair of structural scans and a functional scan that collected about 8 minutes and 40 seconds of resting-state activity. For the structural scan, a Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence was used to acquire a high-resolution 3D T1-weighted structural image with the following parameters: Repetition Time (TR) =2250 milliseconds; Echo Time (TE) =2.99 milliseconds; Inversion Time (TI) =900 milliseconds; flip angle =9 degrees; field of view (FOV) =256mm x 240mm x 192mm; voxel size =1mm isotropic; GRAPPA acceleration factor =2; acquisition time of 4 minutes and 32 seconds. The structural data was used for pre-processing.

The functional, resting-state scan for this study was an 8 minute and 40-second scan where the participant remained awake with their eyes closed. The T2*-weighted fMRI data from the resting-state is acquired during a Gradient-Echo Echo-Planar Imaging (EPI) sequence. A total of 261 volumes were acquired, each containing 32 axial slices (acquired in descending order), slice thickness of 3.7 mm with an interslice gap of 20% (for whole-brain coverage including cerebellum; TR =1970 milliseconds; TE =30 milliseconds; flip angle =78 degrees; FOV =192 mm × 192 mm; voxel-size =3 mm × 3 mm × 4.44 mm).

Three measures of resting-state functional connectivity (RSFC) are the main predictors of the emotion regulation task scores. These measures of connectivity will be extracted using the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). The first two RSFC measures will be seeded between the amygdala and the left and right lateral PFC regions. The third will be between the amygdala and the medial PFC region.

2.2.2 *Emotion Regulation Task*

The emotion regulation task required participants to view 30-second film clips passively or to utilize reappraisal. Participants were instructed to watch 32 film clips that were divided

equally to be of positive, negative, or neutral valence. Participants passively viewed most of the clips; however, for half of the negative film clips only, the participants were instructed to reappraise the clip, in order to reduce their negative emotional response to the clip. Before each individual clip (i.e., trial), the participant was instructed how to respond to the clip (e.g. "WATCH NEUTRAL" or "REAPPRAISE NEGATIVE"). Thus, there were four experimental conditions: (1) watch neutral, (2) watch positive, (3) watch negative, or (4) reappraise negative. There were eight blocks of four clips each; every block was comprised of only one of the above conditions (e.g., all four clips were "WATCH POSITIVE") and after the block of four films, the participant was shown a 30-second calming film clip, which served as a "washout" trial. For the reappraisal condition, participants were instructed to view the negative image and then to think of ways to decrease their negative emotions by reinterpreting what they saw in the film clip. After the clip, the participant rated on a Likert scale of 0 to 100 how negative and how positive they felt after viewing the clip. Following the film clip ratings, there was a manipulation check. The participants rated on a scale of 0 to 100 how effectively they had used the "strategy," of either watching or reappraising the film clip (this variable will be called "effort"). These rating scales were displayed for 10 seconds following the last film clip of each block. In this pre-collected data set, raw affect and effort rating scores for each trial were not included. Rather, average affect and effort ratings for each of the four conditions were provided.

2.3 Measures

2.3.1 *Cattell Intelligence Test*

Estimated intelligence was measured by the Cattell Intelligence test, which was developed to be a culture fair measure of general intelligence (Cattell, 1940). The researchers administered the standard form of the Cattell Culture Fair, Scale 2 Form A. The test consists of 4

timed, nonverbal "puzzles" (i.e., completion, classification, matrices, and conditions). Participants were read the instructions and then engaged in practice trials before working for the allotted time on each puzzle. For each correct answer, the participant scores one point, which is summed for their overall (*g*) score, with a possible maximum of 46. Studies have shown this test to have adequate reliability using a Spearman-Brown reliability coefficient (0.79) and a Cronbach's alpha (0.77; Nenty, & Dinero, 1981).

2.3.2 *Hospital Anxiety and Depression Scale*

The Hospital Anxiety and Depression Scale (HADS) is a brief measure of depressive and anxiety symptoms. There are 14 items, seven of which pertain to anxiety symptoms and seven of which assess depressive symptoms. Each item is scored on a Likert scale of 0-3 and a total score of 11 or higher in one category could be indicative of the presence of a mood disorder. The validity of the HADS has been found comparable to the BDI-II in sensitivity and specificity for detecting major depressive episodes, and the HADS has been shown to have good internal reliability with Cronbach's coefficient alpha (0.878; Kjærgaard, Arfwedson Wang, Waterloo, & Jorde, 2014).

2.4 Preprocessing of Imaging Data

MRI data underwent initial stages of preprocessing prior to being made publicly available (Taylor et al., 2017). I conducted a basic segmentation transformation on the data prior to running it through the CONN Toolbox, which performs final preprocessing procedures before the analysis can begin.

The original MRI data were processed by the CamCAN investigators utilizing several unique pipelines. The structural images had the faces removed in order to protect participant anonymity (Bischoff-Grethe et al., 2007). The structural data were first coregistered to the

functional data using linear transformation and a multi-channel segmentation before being normalized to the MNI template. Finally, each individual's grey and white matter images were smoothed and the ROIs were mapped using the Harvard-Oxford atlas (Desikan et al., 2006). The functional images were unwarped (utilizing the field-map images), motion and slice-time corrected and then normalized to MNI space.

I ran the processed data through the CONN toolbox, which includes several additional pre-processing steps (Whitfield-Gabrieli, & Nieto-Castanon, 2012). The CONN processing uses realignment, and smoothing (8-mm FWHM Gaussian filter), through SPM8 default parameter choices. The CONN toolbox uses the subjects' T1 structural scans to create masks for white-matter and Cerebral Spinal Fluid (CSF) and then uses these masks with the T2 functional data to correct for motion and noise. The BOLD data are corrected using subject-specific structural masks and corrected for predicted motion and time. CONN also utilizes voxel-to-voxel BOLD signal correlation values for temporal preprocessing as well as to help correct for CSF-related noise. This toolbox is then able to analyze the co-registered T1 and T2 data to give subject-specific Functional Connectivity (FC) measures between Harvard-Oxford atlas-based ROIs for analyses.

2.4.1 ROIs

The Regions of Interest (ROIs) are defined as the right and left dorsolateral prefrontal cortex (l-dlPFC & r-dlPFC, respectively), the medial prefrontal cortex (mPFC), and the bilateral amygdala. The ROIs for the mPFC and both the right and left dlPFC are defined within the CONN Toolbox using the Harvard-Oxford Atlas (Whitfield-Gabrieli, & Nieto-Castanon, 2012). For the amygdala ROIs, a bilateral amygdala mask was created using FSLview to conjoin the left and right amygdala structural regions as defined by the Harvard-Oxford atlas in MNI space. The

functional connectivity measures from mPFC, r-dlPFC, and l-dlPFC to the bilateral amygdala will be extracted using the CONN Toolbox for each subject. These ROI-based RSFC measures will serve as one the predictors for the overall model.

2.5 Data Analysis Plan

The current study aims to explore how age moderates the association between three RSFC networks (i.e., mPFC with the bilateral amygdala, r-dlPFC with the bilateral amygdala, l-dlPFC with the bilateral amygdala), and ratings of positive and negative affect after reappraisal. I included the average respective (negative or positive) affect scores from the "neutral watch" condition to serve as a baseline from which I expect to see changes due to reappraisal. I used the CONN toolbox to extract the functional connectivity measures between the ROIs (defined above) from the resting state scan as the main predictor variables. There are three models, each with a unique ROI to amygdala RSFC measure, which was used as the predictor. The RSFC predictor will be included along with age, the control mentioned above, and the interaction term of RSCF and age, in order to test if age is a moderator of the association between resting-state activity and negative and positive affect outcomes. The hypotheses will be tested using regression models after some preliminary analyses. All of these analyses will be run in SPSS.

2.5.1 Preliminary Analysis

I first examined the distributions of all study variables for normality; the two measures of positive affect (in the watch and the reappraisal conditions) both had significant skew and were logarithmically transformed to approximate normality. This is most likely due to the fact the ratings tended to cluster around zero. No outliers needed to be removed. Next, I ran a series of correlations to see which variables were related and should be controlled for in the final model.

I selected several variables as potential covariates because they are associated with emotion regulation success. First was the affect for the negative watch condition to serve as the baseline for the reappraisal condition as described above. Another covariate was the instruction adherence to measure effort and subjective rating of reappraisal efficacy. The Cattell Intelligence test will be used to account for cognitive ability, which has been associated with successful reappraisal (Winecoff et al., 2011). Finally, I also included income as individuals with higher income tend to have higher emotion regulation success (Côté, Gyurak, & Levenson, 2010).

2.5.2 Primary Analysis

In order to test if age will moderate the associations between RSFC and affect scores, regression models were run. I controlled for any variables that were found to be significantly correlated with the outcome measures or age in the preliminary analysis. To account for the fact there was no baseline measure of negative affect, the negative ratings of a neutral film were included as a baseline measure used in each model. This regression was be run using the following equation:

H1:

ER = (mPFC-AMY)RSFC x Age x Baseline(Watch)

ER = (mPFC-AMY)RSFC x Age x Baseline(Watch) x (AGExRSFC)

Our hypothesis is that in this model the moderator will not significantly improve the model fit and that the mPFC to amygdala RSFC predicts negative affect after reappraisal, regardless of age. I will run the above equation as a comparison between a model with a moderator variable of age and one without, with the prediction that the moderator inclusion will not significantly improve the model.

H2:

ER = Age x [l-dlPFC-AMY]RSFC x Baseline(Watch) x (AGExl-[l-dlPFC-AMY]RSFC)

ER = Age x [r-dlPFC-AMY]RSFC x Baseline(Watch) x (AGExl-[r-dlPFC-AMY]RSFC)

The second hypothesis that I will be testing is that the association between right and left dlPFC-Amygdala RSFC and affect post reappraisal is moderated by age, such that for younger adults the dlPFC-Amygdala RSFC will have a strong inverse relationship to successful reappraisal. However, in older age, the strength of the relationship between dlPFC-AMY RSFC and emotion regulation will not be significant.

2.5.3 Power Analyses

A power analysis was conducted using GPower (version 3.1) to confirm that the H2 regression model would have enough power to detect a small effect size. A sensitivity test was run for 299 participants with and an alpha of (0.05), and error margin of (1-B = 0.8). The f^2 ranges for a sample of this size are small (>0.02), medium (>0.15), and large (> 0.35). I found the minimum detectable effect size for this sample with 5 predictors to be in the small range (f^2=0.026). This is with a confidence level of 0.05 since there is no need to correct for family-wise error as it will be only one model with one outcome variable being run at a time. This would be the same for the mPFC hypotheses which predict a non-significant model comparison and while there could still possibly be a very small effect size, the study is well powered enough to detect most effects, and thus can likely support the null.

Results

Preliminary Analyses

Before testing my hypotheses, preliminary analyses were conducted to better understand the distributions of and associations between my independent, dependent, and control variables

(Table 1). While the negative affect scores were normally distributed, the positive affect scores were skewed to the right, thus requiring logarithmic transformations. To test if emotion ratings after the reappraisal task differed from emotion ratings during the baseline watch condition, I ran a paired samples t-test between these scores. Results indicated a significant difference in positive affect ratings, such that the watch ratings (M = 2.34, SD = 1.25) were lower than the reappraisal ratings (M = 2.51, SD =1.36; $t(296) = -3.66$, $p < 0.001$). For the negative affect ratings, there was no significant difference between the watch (M = 7.10, SD = 1.67) and reappraisal conditions (M = 7.15, SD =1.738; $t(297) = -0.68$, $p = 0.50$).

Pearson correlations were run between the positive and negative affect ratings and all of the independent (i.e., age and RSFC measures) and control variables. Results indicated significant positive correlations between post-reappraisal positive affect and age and Instruction Adherence (Table 2). This suggests that older adults and participants who believed they followed task instructions rated the video clips more positively. Age and Instruction adherence were significantly inversely correlated, suggesting older adults reported more difficulty following experiment instructions than younger participants.

Primary Analyses

First, I tested my hypothesis that the association between the mPFC-amygdala RSFC and affect would not be significantly moderated by age. As expected, the interaction effect between the mPFC-Amygdala RSFC and age was not significantly associated with either negative or positive affect in the reappraisal condition. However, contrary to expectations the mPFC-amygdala RSFC was not a significant predictor of negative or positive affect following the reappraisal condition (Tables 11-14).

I then tested if results changed when control variables (i.e., income, intelligence, and

instruction adherence) were added to the models predicting affect from mPFC-amygdala RSFC. Neither mPFC-amygdala RSFC nor the interaction between mPFC-Amygdala RSFC and age were significant predictors of negative or positive affect after reappraisal (Tables 15-18).

Next, I tested if age moderated the association between dlPFC-amygdala activity and affect. Two RSFC scores measured connectivity between the right dlPFC-amygdala and the left dlPFC-amygdala. Since there were two outcomes (i.e., positive and negative affect in the reappraisal condition), four models were run (i.e., two predictors for two outcomes). Results indicated that the interactions between age and the right and left dlPFC-amygdala RSFC were not significant predictors of negative affect (Tables 3 & 4). However, there were significant interactions between age and both right and left dlPFC for predicting positive affect (Tables 5 & 6).

Next, I added the control variables (i.e., income, intelligence, and instruction adherence) to test if the interaction between age and dlPFC-amygdala RSFC in association with PA was still significant (Tables 7-10). There was a significant interaction effect between left and right dlPFC-amygdala with age when predicting positive affect. To illustrate the nature of the moderator effect, the associations between the right dlPFC-amygdala RSFC (Figure 2) and left dlPFC-amygdala RSFC (Figure 3) and positive affect were modeled for younger, midlife, and older adults. As predicted, stronger negative dlPFC-amygdala RSFC is a significant predictor of positive affect in younger adults (~33 years old) and in midlife adults (~54 years old). In contrast, for older adults (~72 years old), the association between dlPFC and the amygdala had no significant association between RSFC and positive affect (left dlPFC R = 0.08; right dlPFC R = 0.08).

Discussion

This study determined how the mPFC-amygdala and dlPFC-amygdala RSFC predicted behavioral indicators of reappraisal success across the adult lifespan. The hypothesis that age would moderate the association between dlPFC-Amygdala RSFC and reappraisal success was partially supported. A stronger negative dlPFC-amygdala resting association was associated with greater positive affect after reappraisal for younger and middle-aged adults but not for older adults. My expectation that the mPFC-amygdala RSFC would be associated with reappraisal success regardless of age was not supported.

Strength of the dlPFC-Amygdala Connectivity and Reappraisal Outcomes

Our results suggest that dlPFC-amygdala activity at rest may be a predictor of emotion regulation in younger and midlife adults but that dlPFC-amygdala activity may be less predictive of emotion regulation outcomes in later life. Our results are consistent with previous studies that showed that for older adults, the dlPFC was not as active during reappraisal as in middle and younger-aged adults (Allard and Kensinger, 2014, Urry et al., 2006; Opitz, Rauch, Terry, & Urry, 2012). While most previous studies on the association between RSFC the PFC and the amygdala, and reappraisal, have mostly compared younger adults to older adults, one study examined middle-aged adults (Pico-Perez et al., 2018). Middle-aged adults with strong negative connectivity between the amygdala and frontal regions - such as the dlPFC - reported greater use of reappraisal on a self-report questionnaire (Pico-Perez et al., 2018). My study extends the findings evident in these previous studies that younger and midlife adults with greater negative dlPFC-amygdala RSFC have more reappraisal task success and further demonstrates this trend is not the case for older adults.

mPFC-Amygdala RSFC not a Predictor of Affect after Reappraisal

This study failed to find a significant association between the mPFC-amygdala RSFC and affect after reappraisal. Previous studies have had mixed findings regarding the mPFC's role in reappraisal, with a major meta-analysis finding that the mPFC was inconsistently active during reappraisal (Buhle et al., 2014). In this meta-analysis, only 1 of 838 coordinates was found to be active in the vmPFC seed sphere during reappraisal tasks across multiple studies. However, some studies have found the mPFC to correlate with HRV, which is a physiological analog of ER (Sakaki et al., 2014; Steinfurth et al., 2018). The vmPFC was also related to normative cortisol recovery levels after experiencing a negative stressor (Urry et al., 2006), suggesting that the mPFC is associated with physiological measures of ER.

One reason that my hypothesis may have been unsupported is that the mPFC is involved in the default mode network (DMN, Davey, Pujol, & Harrison, 2016). The DMN is active at rest (Raichle, M. E. (2015). Meanwhile, the amygdala is not meant to be active at rest, and hyperactivity of the amygdala at rest is indicative of some psychological disorders (Pinkham et al., 2015). Thus, resting-state measures of the mPFC-amygdala may not hold to the typical predicted relationship of mutual deactivation during rest, thus changing the RSFC measure.

Limitations

The project involved secondary data analysis and thus the methodology was not ideally aligned to test this study's aims. For example, baseline affect was not assessed prior to the reappraisal condition, which would have allowed us to measure the change in affect, which should be smaller if reappraisal was successful. Another limitation is that the data were preprocessed by the CamCAN investigators (Taylor et al., 2017). The preprocessing of the T1 structural images was conducted without factoring in age norms, which is problematic because as

the brain ages it can undergo significant physical changes, such as deterioration, shrinking frontal regions, and enlarged perivascular spaces,

Future Directions

While my results have elucidated the association between age and RSFC of dlPFC-amygdala with reappraisal success, a great deal more can be done with this data set alone. Further analysis and modeling of the age and RSFC interaction may be able to show precisely around the age at which the interaction with age and connectivity begins to occur.

There are regions other than the mPFC, dlPFC, and amygdala involved in reappraisal and emotion regulation. Utilizing the CamCAN sample, examining the RSFC specifically of the ventral mPFC to amygdala could be explored using this model to see if this particular region of the mPFC has a predictive relationship with post reappraisal affect. The ventral lPFC has also been shown to be involved in the reappraisal process (Buhle et al., 2014) and thus may also be worthy of investigation. Other regions could also be explored such as a different medial region, the anterior cingulate cortex, (ACC; Allard & Kensinger, 2014) or a different lateral region: the inferior frontal gyrus (IFG) which has also been shown to have differential connectivity with age (Winecoff, LaBar, Madden, Cabeza, & Huettel, 2011). Age may moderate those relationships as well, thus, this model design could be used to test other regions' RSFC following a similar logic. It may also be beneficial to test the inter connectivity of these regulating regions' (lPFC, mPFC, & IFG) with one another, rather than their relationship with the amygdala at rest.

The hope of these future studies is to understand better which clinical approaches may be most effective for older adults based on neural evidence. This study revealed there is a change in reappraisal-related regions based on age, and if we can further clarify this shift, it may help to inform our clinical approaches to working with older adults. With life expectancy increasing,

more older adults may need therapy, and thus determining which approaches may be most efficacious would be a significant boon for the clinical community.

APPENDIX A

TABLES

Table 1.

Descriptive Statistics for Independent and Dependent Variables and Covariates

Variable	Mean	SD
Intelligence	32.32	96.88
RSFC left-dlPFC	-0.09	0.18
RSFC right-dlPFC	-0.10	0.19
RSFC mPFC	0.15	0.19
Instruction Adherence	6.82	1.94
Positive Affect for Negative Watch Condition	2.35	1.25
Negative Affect for Negative Watch Condition	7.1	1.67
Positive Affect for Reappraisal Condition	2.5	1.36
Negative Affect for Reappraisal Condition	7.15	1.74

Table 2

Correlations between Independent and Dependent Variables and Covariates

Variables	IQ	lPFC	rPFC	mPFC	P.W.	N.W.	P.R.	N.R.	Ins.	Inc.
Age	-0.039	-0.054	-0.021	0.001	0.498**	0.094	0.466**	0.091	-0.216**	0.037
IQ	1	0.038	-0.011	-0.009	0.019	0.068	0.009	0.053	-0.216**	0.037
lPFC	-	1	0.688**	0.100	0.011	-0.014	-0.036	-0.017	0.049	0.009
rPFC	-	-	1	0.071	0.048	-0.044	-0.011	-0.049	0.004	0.139*
mPFC	-	-	-	1	0.065	0.057	0.042	0.043	-0.035	0.102
P.W.	-	-	-	-	1	0.166**	0.822**	0.204**	-0.087	0.026
N.W.	-	-	-	-	-	1	0.147*	0.791**	0.164**	-0.08
P.R	-	-	-	-	-	-	1	0.073	0.072	0.050
N.R	-	-	-	-	-	-	-	1	0.139*	0.050
Ins.	-	-	-	-	-	-	-	-	1	-0.032
Inc.	-	-	-	-	-	-	-	-	-	1

IQ= Cattell Intelligence Score, lPFC = left dlPFC, rPFC= right dlPFC, mPFC= medial PFC, PW= Positive Affect for Negative Watch Condition, N.W.= Negative Affect for Negative Watch Condition, P.R.= Positive Affect for Negative Reappraisal Condition, N.R. Negative Affect for Negative Reappraise Condition, Ins.= Instruction Adherence, Inc.= Income

Table 3

Negative Affect Predicted by Age and left dlPFC - Amygdala RSFC

n= 297	*b*	*SE*	*t*	*β*	*p*
Age	0.001	0.004	0.382	0.015	.703
RSFC	-0.048	0.338	-0.143	-0.005	.886
Age*RSFC	-0.001	0.018	-0.071	-0.003	.943
N.W. (Negative Affect)	0.820	0.037	21.900	0.789	<.001

$R^2 = 0.626$, $p < .001$

Table 4

Negative Affect Predicted by Age and right dlPFC - Amygdala RSFC

n= 297	*b*	*SE*	*t*	*β*	*p*
Age	0.002	0.004	0.489	0.019	.625
RSFC	-0.131	0.333	-0.393	-0.014	.695
Age*RSFC	0.003	0.017	0.188	0.008	.851
N.W. (Negative Affect)	.820	0.038	21.853	.790	<.001

$R^2 = 0.017$, $p = 0.175$

Table 5

Positive Affect Predicted by Age and left-dlPFC - Amygdala RSFC

n= 297	*b*	*SE*	*t*	*β*	*p*
Age	0.003	0.001	2.470	0.101	.014
RSFC	-0.115	0.088	-1.305	-0.043	.193
Age*RSFC	0.010	0.005	2.142	0.077	.033
N.W. (Positive Affect)	.822	0.040	20.745	0.787	<.001

$R^2 = 0.223$, $p < 0.001$

Table 6

Positive Affect Predicted by Age and right-dlPFC - Amygdala RSFC

n= 294	*b*	*SE*	*t*	*β*	*p*
Age	0.003	0.001	2.566	0.106	.011
RSFC	-0.137	0.087	-1.579	-0.052	.115
Age*RSFC	0.010	0.004	2.280	0.083	.023
N.W. (Positive Affect)	0.823	0.040	20.789	.789	<.001

$R^2 = 0.225$, $p < 0.001$

Table 7

Negative Affect Predicted by Age and left-dlPFC - Amygdala RSFC with Controls

n= 296	*b*	*SE*	*t*	*β*	*p*
Age	0.000	0.005	-0.005	0.000	.996
RSFC	0.039	0.343	0.115	0.004	.909
Age*RSFC	-0.006	0.018	-0.334	-0.013	.739
N.W. (Negative Affect)	0.822	0.038	21.492	0.790	<.001
Instruction Adherence	0.012	0.034	0.358	0.013	.720
Intelligence	-0.004	0.014	-0.303	-0.015	.762
Income	-0.052	0,042	-1.234	-0.045	0.218

$R^2 = 0.634$, $p < 0.001$

Table 8

Negative Affect Predicted by Age and right-dlPFC - Amygdala RSFC with Controls

n= 296	*b*	*SE*	*t*	*β*	*p*
Age	0.000	0.005	0.099	0.005	.921
RSFC	-0.019	0.337	-0.058	-0.002	.954
Age*RSFC	0.003	0.017	0.178	0.007	.859
N.W. (Negative Affect)	0.824	0.038	21.532	0.792	<.001
Instruction Adherence	0.011	0.033	0.317	0.012	.751
Intelligence	-0.005	0.013	-0.370	-0.019	.712
Income	-0.050	0.042	-1.196	-0.043	.233

$R^2 = 0.634$, $p < 0.001$

Table 9

Positive Affect Predicted by Age and left-dlPFC - Amygdala RSFC with Controls

n= 296	*b*	*SE*	*t*	*β*	*p*
Age	0.002	0.001	1.871	0.092	.062
RSFC	-0.143	0.088	-1.626	-0.053	.105
Age*RSFC	0.010	0.005	2.219	0.081	.027
N.W. (Positive Affect)	0.797	0.040	19.969	0.763	<.001
Instruction Adherence	0.028	0.009	3.326	0.1112	.001
Intelligence	-0.005	0.004	-1.436	-0.067	.152
Income	0.013	0.011	1.218	0.040	.224

$R^2 = 0.700$, $p < 0.001$

Table 10

Positive Affect Predicted by Age and right-dlPFC - Amygdala RSFC with Controls

n= 296	*b*	*SE*	*t*	*β*	*p*
Age	0.003	0.001	2.071	0.103	.039
RSFC	-0.156	0.086	-1.811	-0.059	.071
Age*RSFC	0.011	0.004	2.572	0.093	.011
N.W. (Positive Affect)	1.837	0.092	20.010	0.763	<.001
Instruction Adherence	0.030	0.008	3.538	0.118	<.001
Intelligence	-0.005	0.004	-1.408	-0.065	.160
Income	0.011	0.011	1.043	0.034	.298

$R^2 = 0.700$, $p < 0.001$

Table 11

Negative Affect Predicted by Age and mPFC - Amygdala RSFC

n= 297	*b*	*SE*	*t*	*β*	*p*
Age	0.000	0.004	-0.103	-0.005	.918
RSFC	-0.050	0.339	-0.147	-0.005	.883
Age*RSFC	0.013	0.018	0.749	0.034	.454
N.W. (Negative Affect)	0.819	0.037	21.950	0.789	<.001

$R^2 = 0.627$, $p < .001$

Table 12

Negative Affect Predicted by Age and mPFC - Amygdala RSFC without Interaction

n= 297	*b*	*SE*	*t*	*β*	*p*
Age	0.002	0.003	0.459	0.016	.646
RSFC	-0.019	0.336	-0.055	-0.002	.956
N.W. (Negative Affect)	0.820	0.037	21.997	0.790	<.001

$R^2 = 0.626$, $p < .001$

Table 13

Positive Affect Predicted by Age and mPFC - Amygdala RSFC

n= 297	*b*	*SE*	*t*	*β*	*p*
Age	0.002	0.001	1.875	0.087	.062
RSFC	-0.016	0.089	-0.179	-0.006	.858
Age*RSFC	-0.003	0.005	-0.589	-0.025	.550
N.W. (Positive Affect)	0.822	0.040	20.506	0.787	<.001

$R^2 = 0.219$, $p < 0.001$

Table 14

Positive Affect Predicted by Age and mPFC - Amygdala RSFC Without Interaction

n= 297	*b*	*SE*	*t*	*β*	*p*
Age	0.002	0.001	1.860	0.071	.064
RSFC	-0.023	0.089	-0.255	-0.008	.799
N.W. (Positive Affect)	.822	0.040	20.552	0.787	<.001

$R^2 = 0.680$, $p < 0.001$

Table 15

Negative Affect Predicted by Age and mPFC - Amygdala RSFC with Controls

n= 296	*b*	*SE*	*t*	*β*	*p*
Age	-0.001	0.005	-0.272	-0.016	.786
RSFC	-0.008	0.340	-0.024	-0.001	.981
Age*RSFC	0.012	0.018	0.685	0.031	.494
N.W. (Negative Affect)	0.822	0.038	21.581	0.790	<.001
Instruction Adherence	0.011	0.033	0.334	0.013	.739
Intelligence	-0.005	0.013	-0.337	-0.017	.736
Income	-0.049	0.042	-1.169	-0.042	.243

$R^2 = 0.635$, $p < 0.001$

Table 16

Negative Affect Predicted by Age and mPFC - Amygdala RSFC without Interaction

n= 296	*b*	*SE*	*t*	*β*	*p*
Age	0.000	0.005	0.061	0.003	.952
RSFC	0.020	0.337	0.030	0.002	.952
N.W. (Negative Affect)	0.823	0.038	21.633	0.791	<.001
Instruction Adherence	0.011	0.033	0.326	0.012	.745
Intelligence	-0.005	0.013	-0.352	-0.018	.725
Income	-0.051	0.042	-1.212	-0.043	.226

$R^2 = 0.634$, $p < 0.001$

Table 17

Positive Affect Predicted by Age and mPFC - Amygdala RSFC with Controls

n= 296	*b*	*SE*	*t*	*β*	*p*
Age	0.002	0.001	1.617	0.088	.107
RSFC	0.005	0.088	0.060	0.002	.952
Age*RSFC	-0.002	0.005	-0.531	-0.022	.596
N.W. (Positive Affect)	0.798	0.041	19.699	0.764	<.001
Instruction Adherence	0.030	0.009	3.489	0.119	.001
Intelligence	-0.004	0.004	-1.076	-0.050	.283
Income	0.009	0.011	0.805	0.027	.421

$R^2 = 0.693$, $p < 0.001$

Table 18

Positive Affect Predicted by Age and mPFC - Amygdala RSFC without Interaction

n= 296	*b*	*SE*	*t*	*β*	*p*
Age	0.002	0.001	1.547	0.075	.123
RSFC	0.000	0.088	-0.05	0.000	.996
N.W. (Positive Affect)	0.798	0.040	19.718	0.764	<.001
Instruction Adherence	0.030	0.009	3.499	0.119	.001
Intelligence	-0.004	0.004	-1.069	-0.050	.286
Income	0.009	0.011	0.838	0.028	.403

$R^2 = 0.693$, $p < 0.001$

APPENDIX B

FIGURES

Figure 1

The Emotion Regulation Task Structure

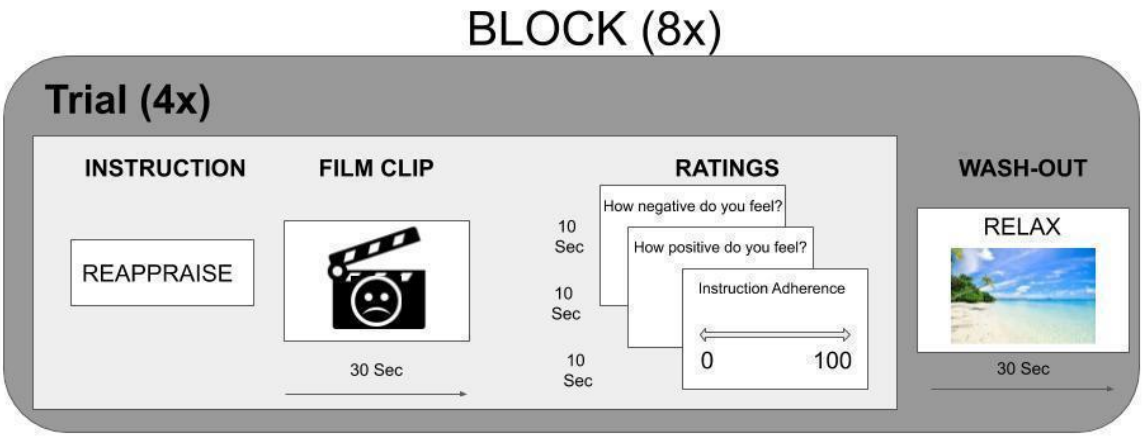
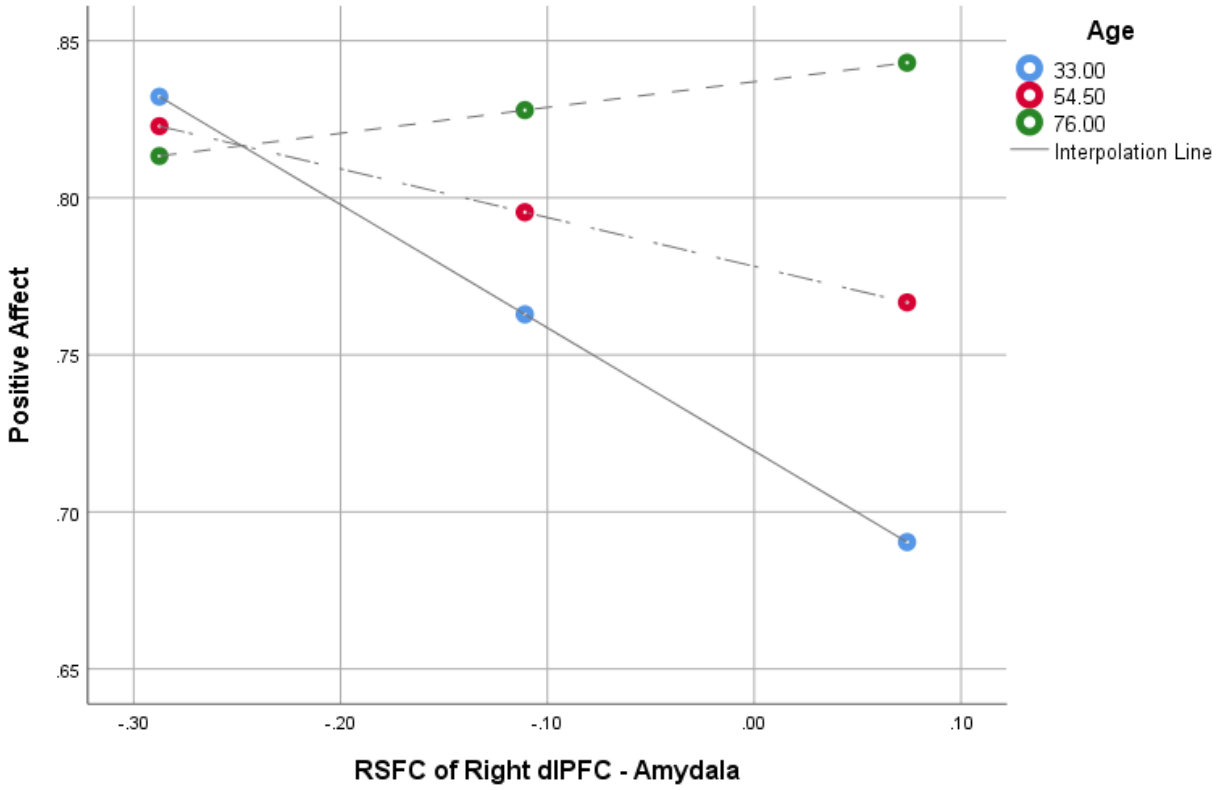


Figure 2

Graph of Interaction of Age and Right dlPFC Effect.



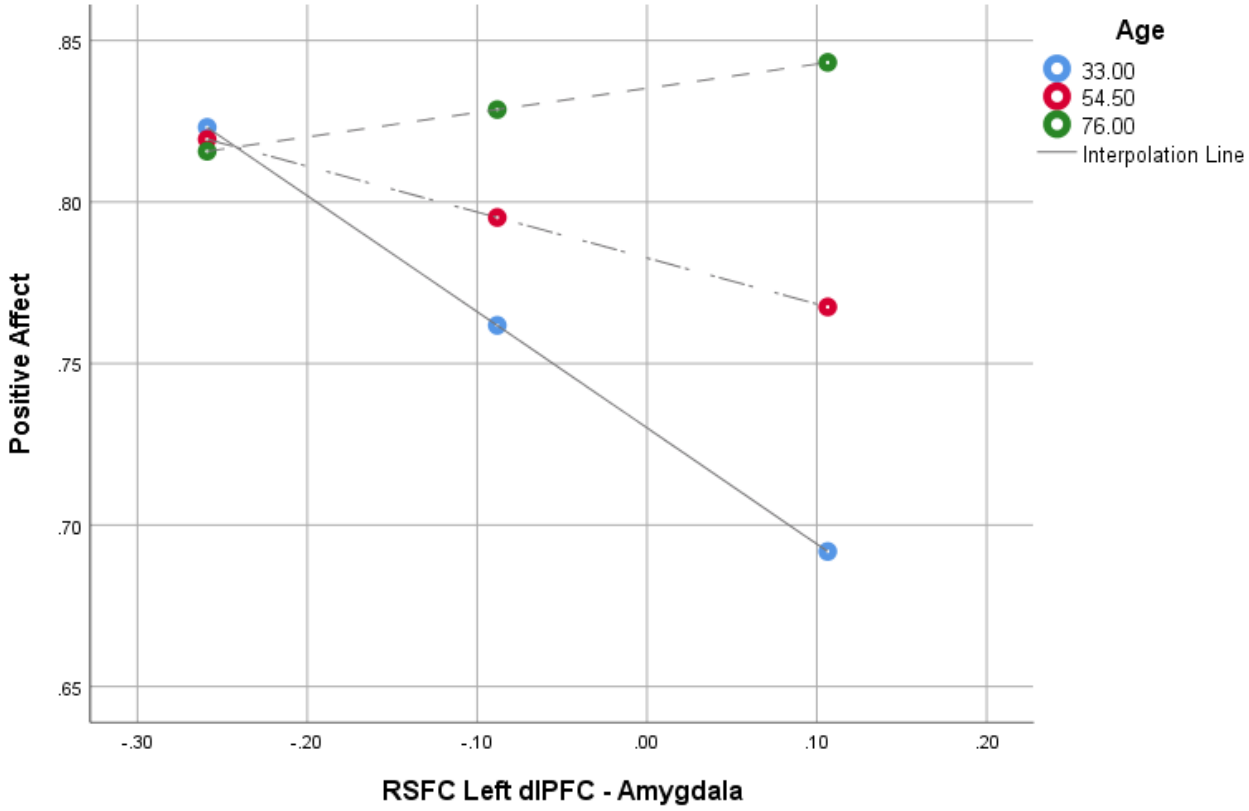
Blue: Adults with the average age of 33

Red: Adults with the average age of 54

Green: Adults with the average age of 72

Figure 3.

Graph of Interaction of Age and Left dlPFC Effect.



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