Investigating the association of resting-state brain effective connectivity with basic negative emotions

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Abstract

Emotions are the foundational elements of mental health. Basic negative emotions have an assertive significant role in personality building while their unrestrained form can lead to mental health disorders and physical illnesses. The self-reported measures of negative emotions are usually associated with persistent feelings and hence may reflect trait-like negative emotions. Examining the association of brain intrinsic effective connectivity with the self-reported basic negative emotions can provide the basis of trait-like personality. The current study focuses on investigating the association of resting-state brain effective connectivity with the self-reported scores of all three basic negative emotions - anger, fear, and sadness. The relationship of effective connectivity with low and high levels of negative emotions was determined. The dataset comprises preprocessed resting-state fMRI scans and NIH emotion battery for self-reported basic emotions scores, of 1079 young healthy adults from Human Connectome Project (HCP). Subject-specific effective connectivity was discovered using spectral dynamic causal modelling, and the group-level effective connectivity association with the three basic emotions were examined using parametric empirical Bayes. The results revealed that the limbic-cortical connectivity from right amygdala (rAMG) to posterior cingulate cortex (PCC) could be the potential biomarker for heightened self-report negative emotions and hence could reflect trait-like personality related to negative emotions. The high anger-affect and high sadness have the strongest negative association with the inhibitory connection of rAMG to PCC while high fear-affect have the strongest negative association with inhibitory left anterior insula to PCC connectivity along with the second strongest negative association with inhibitory rAMG to PCC connectivity. The results of these association analyses may be used for the comparative analysis of causal brain connectivity in mental health disorders and may also represent the trait-like personality related to negative emotions.

Introduction

Emotions are the subjective feelings or thoughts of an individual which usually arise from past experiences and impact their behavior influencing general health and well-being. There are four basic human emotions - happiness, fear, anger and sadness (Jack et al., 2014). The response to the aversive environmental conditions or surrounding situation arises due to negative emotions of anger, fear, and sadness. Negative valence systems are positively associated with psychological health (Coifman et al., 2016) and their improper regulation leads to mental health disorders (Berking & Wupperman, 2012; Williams, 2017) and physical illnesses (Wiech & Tracey, 2009). Effective emotion regulation is essential for psychological well-being and this capacity is disrupted in numerous psychiatric disorders. Emotional measurement is an essential tool to assess emotion regulation mechanism. The measuring of emotion can be done in a variety of ways including behavior observation such as vocal and facial expressions, physiological attributes such as blood pressure, brain activity and self-reported measures (Mauss & Robinson, 2009). The self-reported measures of emotions usually involve questions related to persistent feelings over a period of time, therefore, could indicate `trait-like' negative emotions rather than the `state-like' or transient negative emotions. Such questionnaires revolve around the recent past such as last one week and/or life-long experiences. Some questionnaires ask the participants to recall certain past events and relive the experiences while some generally ask them to evaluate their feelings from the past. These measures may capture the entrenched patterns or ways of perceiving and interpreting situations.

The neurological underpinnings of the trait-like measures of personality related to basic negative emotions have been investigated using measures of brain connectivity derived from resting state functional MRI. There have been a few studies investigating the functional connectivity – defined as the statistical dependencies among observed neurophysiological responses – of basic emotions which have relied on the induction of emotions using naturalistic stimuli, either visual or auditory (Morawetz et al., 2016; Raz et al., 2016; Saarimäki et al., 2022). Emotion induction has a different meaning than emotion measurement. In emotion induction, the emotional state of a being is altered by changing environmental conditions while emotion measurement is the assessment of someone's feelings either transient or persistent. Functional connectivity association was also explored with the self-report negative trait emotions (Fulwiler et al., 2012; Kim et al., 2022; Sorella et al., 2022; Sylvester et al., 2012; Weathersby et al., 2019; Zidda et al., 2018). A few studies investigated the effective connectivity – defined as the influence one neural system exert over another, either synaptically or population-wide (Karl J. Friston, 2011) – of basic emotions involving emotion induction mechanism (de Marco et al., 2006; Dima et al., 2011; Mazzola et al., 2020; Seok & Cheong, 2019; Sladky et al., 2015). Recently, a study was conducted to examine the effective connectivity associated with trait somatic anxiety which yielded that there was improved top-down effective connectivity at high fear-related somatic arousal (Bouziane et al., 2022). It is crucial to understand the underlying neural mechanism of basic negative emotions – anger, fear, and sadness - in healthy subjects as it may provide comparative results to comprehend mental health disorders, however, there is no such investigation present in the previous literature. This motivated us to investigate the underlying brain representation of the self-reported basic negative emotions.

In this paper, our objective is to determine the relationship between effective connectivity of the brain regions of the three major resting-state networks—the executive, default mode, and salience networks— and the self-reported basic negative emotions of anger, fear, and sadness. The high levels of negative emotions usually involve disrupted emotion regulation, more inward thoughts causing a self-referential loop preventing cheerful or balanced outlook towards the external world or situations and improper emotional salience processing and subjective feelings. In the negative valence system, given the importance of amygdala and medial prefrontal cortex and their connectivity for emotion regulation (Banks et al., 2007; Berboth & Morawetz, 2021; Denny et al., 2015; Hare et al., 2005; Underwood et al., 2021), posterior cingulate cortex for self-referential mechanism (Brewer et al., 2013; Davey et al., 2016) and anterior insula for salience processing (Craig, 2009; Gu et al., 2013; Park & Tallon-Baudry, 2014; Underwood et al., 2021), we hypothesize that the limbic-cortical causal connections of these regions would show associations with the self-reported negative emotions.

Methods

fMRI Dataset

The resting-state fMRI scans and emotional function data of 1079 healthy young adults (females = 584, age: 22-35 years, mean age: 28.78) was derived from the Human Connectome Project (HCP) (Van Essen et al., 2013). The resting-state fMRI data was collected using Siemens 3T scanner. The acquisition parameters included TR=720 ms, TE=33.1 ms, 1200 frames per run, flip angle = 52 deg, FOV = 208x180 mm. The data was already preprocessed using fMRI volume minimal preprocessing pipeline of HCP (Glasser et al., 2013). The head motion and physiological noise correction was performed using nuisance regression, with six parameter estimates (translational and rotational) from rigid body transformation (downloaded from HCP) and CSF and WM timeseries as regressors.

Psychometric measures of emotional function

The emotion measures consist of NIH Toolbox Emotion Battery (Babakhanyan et al., 2018). Only self-report emotional function measurements are included in the NIH Toolbox. It consists of positive and negative subdomains of emotional health including measures of negative affect (anger, fear, and sadness), psychological well-being (positive affect, general life satisfaction, meaning and purpose), stress and self-efficacy (perceived stress and self-efficacy) and social relationships (social support, companionship, social distress). Our focus was on basic negative emotions, therefore utilized only scores of negative affect subdomain.

NIH Toolbox measures anger using anger-affect survey, anger-hostility survey, and anger-physical aggression survey. The self-report measure of anger-affect assesses anger as an emotion while anger-hostility and anger-physical aggression assesses hostility and aggression. Likewise, the toolbox measures fear using fear-affect survey and fear-somatic arousal survey which assesses fear as an emotion and somatic symptoms respectively. We used only relevant scores of anger-affect and fear-affect. The participants were asked questions about their emotional experience during the past 7 days prior the scan. Each emotion measurement was assessed using a computerized adaptive test (CAT) comprised of 4-6 items or questions derived from a question bank. The participant responds to each item by selecting one out of five response choices with raw scores 1 to 5 where high score denotes a strong emotion. The raw scores are summed up and converted into standard T-scores that are based on US healthy population. For this scale, the mean T-score is 50 with a standard deviation of 10. The scores below the mean ($T \leq 40$) indicate low levels while above the mean ($T \geq 60$) indicate high levels of fearful, angry, and sad feelings.

Regions of interest selection

Regions of interest (ROIs) spanning the three large-scale resting-state networks, default mode network (DMN), salience network (SN) and executive network (EN), were selected based on their significance in the emotion processing and emotion regulation. The chosen ROIs are posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC) and bilateral hippocampus (lHP and rHP) for the DMN, dorsal anterior cingulate cortex (dACC), bilateral anterior insula (lAI and rAI) and bilateral amygdala (lAMG and rAMG) for the SN, and bilateral dorsal lateral prefrontal cortex (lDLPFC and rDLPFC) for the EN. The regional centroids were identified using associativity test maps of the regions from neurosynth.org. The associativity test maps consist of the z-scores indicating the non-zero association between the ROI and voxel activation. These maps were utilized to locate the centroid of each ROI by identifying the local maxima of the selected cluster in the map (using xjview [https://www.alivelearn.net/xjview]). The spherical regions of 8 mm were selected with the respective centroids (Table 1). To avoid the spheres, of smaller-sized regions, from incorporating voxels outside the anatomical limit of the particular regions, binary masks were created using AAL (Tzourio-Mazoyer et al., 2002) for the amygdala and anterior insula, as well as resting-state network template masks for the hippocampus (Shirer et al., 2012). The time-series extracted from each ROI in the form of the first principal-variate of all the regional voxels timeseries, was used as the observed BOLD signal for the effective connectivity estimation.

Subject-level effective connectivity analysis

The effective connectivity investigation for resting state fMRI of each subject was carried out using spectral DCM (spDCM; (K. J. Friston et al., 2014; Razi et al., 2015)) - a variant of DCM to infer the resting-state or intrinsic effective connectivity among the neural population. DCM is a

Bayesian framework composed of generative models of stochastic neuronal dynamics and hemodynamic response for the observed BOLD signal (K. J. Friston et al., 2003). The fully connected spectral DCM of 11 ROIs was used to estimate the intrinsic effective connectivity using the cross-spectra of the signals. We estimated the 11 x 11 asymmetric matrix for each subject representing effective connectivity between and within networks using spectral DCM. The average percentage of variance explained by the DCM model estimation was used to assess the accuracy of the model inversion. Please refer to the supplementary material for technical details of spDCM.

Association of effective connectivity and basic negative emotions

The subjects were divided into groups (low and high) based on their self-reported emotional scores to perform association analysis of effective connectivity with each emotion. The association analyses were conducted using parametric empirical Bayes (PEB; (Karl J. Friston et al., 2016; Zeidman et al., 2019)). Parametric empirical Bayes for DCM refers to the Bayesian hierarchical model over the parameters that explains the subject-level effects using group-level parameter estimates. The use of the entire posterior density over the parameters from each subject's DCM is the major benefit of PEB over classical hypothesis testing which only uses the expected values of connectivity parameters, discarding the estimated parameter uncertainty. Here, the purpose of using PEB is to model the within-subject connectivity differences in association with subject-specific emotions measures. In this Bayesian GLM, a group-level variable of interest (emotion scores) and any unexplained noise defined as covariates or regressors, were used to model the subject-level parameter estimates (posterior distribution of effective connectivity). The group mean is the first regressor followed by the mean-centered emotion scores. An efficient automatic Bayesian model search was performed using Bayesian model reduction (BMR) algorithm. BMR explores the model space by pruning the connections of the full model to produce reduced models. The reduced models are examined based on log model-evidence, pruning stops when model-evidence cannot be improved further. Bayesian model averaging (BMA) is used to consider parameters from all model variations. BMA averages the models' parameters weighted with their model evidence (Penny et al., 2010). As a result, group-level parameters (the so-called beta-coefficients) are obtained representing the association between effective connectivity and emotional scores. For detailed information on PEB, please refer to the supplementary material.

Results

We report the results of effective connectivity association with self-reported scores of anger-affect, fear-affect and sadness. Most of the self-connections were associated with these scores. In DCM, self-connections are also called intrinsic connections or endogenous connections. These are intra-region connections while between-region connections are called extrinsic connections. In DCM, self-connections are modelled as inhibitory and are log-scaled parameters. They represent inhibitory influence on the region and hence control the sensitivity to the extrinsic connections or input to the region. A positive self-connection represents increased inhibition of external inputs and vice versa. The net effect of input connections from other regions decreases with the increase in the self-connection magnitude.

Statistical analysis of self-reported scores of negative emotions

The subjects were divided into two groups based on their scores category (high, low) for each emotion. Out of total 1079, subjects were excluded from the analysis having moderate scores ($60 > T > 40$) for each emotion. There were 157 and 65 subjects with low (34.44 ± 3.99) and high

(64.65 ± 4.65) anger-affect scores, 103 and 100 subjects with low (35.12 ± 2.67) and high (64.85 ± 4.49) fear-affect scores and 237 and 57 subjects with low (35.84 ± 2.32) and high (64.69 ± 4.82) sadness scores respectively. The correlations between each pair of emotions measures are shown in Figure S1. High anger-affect and high sadness are highly correlated with Pearson's correlation coefficient of 0.91. Interestingly, high fear-affect and low fear-affect were also highly correlated with correlation coefficient of 0.98.

Subject-level effective connectivity

The average variance explained or the DCM model fit to the data over all the subjects was 87.10% with minimum 50% and maximum 97% (Figure S2). These model inversion accuracies represent excellent model fitting. The matrices representing group mean effective connectivity for each emotion category are shown in Figure S3. The most prominent in the mean connectivity is the negative self-connection of left hippocampus for the high anger-affect, high fear-affect, and high sadness.

Association of effective connectivity and self-reported scores of anger-affect

The self-reported high anger-affect was associated with 11 causal connections with strongest positive association of negative self-connection of lAMG and strongest negative association of inhibitory rAMG to PCC connectivity. There were also other negative associations of inhibitory connections of dACC to PCC, rAI to rHP, rHP to rDLPFC, lAMG to rHP and negative self-connection of lHP. Among the other positive associations, there were inhibitory connections of lAI to rDLPFC, dACC to rAMG, rAMG to dACC and negative self-connection of lDLPFC.

The self-reported low anger-affect was also associated with 11 causal connections with strongest positive association of negative self-connection of rAI and strongest negative association of inhibitory lAI to rHP connectivity. Among the other negative associations, there were inhibitory connections of lAI to rAMG, lAMG to rHP, dACC to rHP, dACC to lAMG, excitatory connections of dACC to mPFC, positive self-connection of lAI and negative self-connection of lHP. The positive associations also included inhibitory lAI to PCC and excitatory PCC to lAMG.

The negative self-connection of lHP was negatively associated with both high and low anger-affect simultaneously. The results are illustrated in Figure 1. The brain networks were visualized using the BrainNet Viewer (Xia et al., 2013).

Association of effective connectivity and self-reported scores of fear-affect

The self-reported high fear-affect was associated with 9 causal connections with strongest positive association of self-connection of rHP and strongest negative association of inhibitory lAI to PCC connectivity. Among the other negative associations, there were inhibitory connections of rAMG to PCC, rHP to mPFC and excitatory dACC to rDLPFC. The positive associations also included inhibitory PCC to dACC, excitatory lHP to mPFC and self-connections of dACC and mPFC.

The self-reported low fear-affect was associated with only 4 causal connections with strongest positive association of self-connection of rAI and strongest negative association of self-connection of rHP. The other two included negative association of self-connection of PCC and positive association of inhibitory PCC to lDLPFC connectivity.

The self-connection of rHP was negatively and positively associated with low and high fear-affect respectively. The results are illustrated in Figure 2.

Association of intrinsic effective connectivity with self-reported scores of sadness

The self-reported high sadness was associated with 20 causal connections with strongest positive association of self-connection of dACC and strongest negative association of inhibitory rAMG to PCC connectivity. The other negative associations included inhibitory connections of rHP to PCC, lAMG to rHP, rHP to mPFC, dACC to lDLPFC, excitatory connections of dACC to rDLPFC, rAI to dACC, rAI to rDLPFC, self-connection of rDLPFC and self-connection of lHP. Among the other positive associations, there were inhibitory connection of dACC to rAMG, excitatory connections of PCC to dACC, lHP to mPFC, lAI to lAMG and self-connections of PCC, lDLPFC, rAI and rHP.

The self-reported low sadness was associated with only 3 causal connections with strongest positive association of self-connection of rAMG and strongest negative association of self-connection of lAMG. The only other negative association was inhibitory lAI to lHP connectivity. The results are illustrated in Figure 3.

Discussion

This study investigated the association of self-reported basic negative emotions (anger, fear, sadness), with the effective connectivity between brain regions spanning the three large-scale resting-state networks namely, default-mode, salience, and executive networks. The study is based on a large-scale data consisting of the resting state fMRI scans of 1079 healthy subjects acquired from Human Connectome Project (HCP) which were divided into two groups based on their score category (high, low) for each emotion. Some participants were not a part of either group as they had moderate scores, neither high nor low.

Our findings revealed the significant contribution of limbic-cortical connectivity of amygdala to posterior cingulate cortex in high anger-affect, high fear-affect, and high sadness. According to our results, the influence of right amygdala over posterior cingulate cortex may be the important neural mechanism for the higher negative emotions (Figure 4). The high anger-affect and sadness have the strongest negative association with inhibitory rAMG to PCC connectivity while high fear-affect have the strongest negative association with inhibitory lAI to PCC connectivity and second strongest negative association with inhibitory rAMG to PCC connectivity.

The PCC is well-acknowledged for its contribution in social cognition (Mars et al., 2012), self-reflection (Brewer et al., 2013) and interaction mechanisms between memory and emotions (Maddock et al., 2003). Among the DMN regions, self-referential processes are driven by PCC activity while modulated by mPFC (Davey et al., 2016). The negative affect is typically related to exaggerated self-referential activity, the overindulgence of one's thoughts about the self may lead to the negative interpretation of the situations. The involvement of PCC in driving self-referential processes may be the reason for negative association of right amygdala to PCC and left anterior insula to PCC connectivity with the high negative emotions. Amygdala is a salient brain region for emotion generation and emotion regulation. It interacts with various subcortical and cortical regions to augment the processing of emotions. It was previously recognized for its prominent role in fear but is now regarded as a brain region which is involved in other negative emotions as well. The resting state functional connectivity of PCC and right amygdala has shown to be negatively correlated in the depressed patients in a previous study (Chase et al., 2014) that may be considered similar to the current study where there was a negative association of inhibitory extrinsic connection of right amygdala to PCC with high sadness scores and high anger-affect scores. The increase in the inhibitory connection from right amygdala to PCC is related to the decrease in sadness and anger-affect. These association results indicating the decreased influence of amygdala over PCC may suggest the potential prevention of outward thought processes and excess of self-relevant thoughts that result in disruption of emotion regulation. An earlier resting-state study, indicated negative correlation of trait-anger with functional connectivity between right amygdala and PCC while anger-control showed positive correlation (Fulwiler et al., 2012). Also, some neuroticism studies showed increased PCC activity (Dong et al., 2020) and increased functional connectivity between amygdala and PCC (Wang et al., 2018) which represent the significance of PCC in negative affect. In line with this, our results also showed negative association of self-connection of PCC with low fear-affect while positive association of self-connection of PCC with high sadness. The negative self-connection of PCC i.e., decrease in its inhibition is associated with the increase in sadness and fear-affect. Taken together, the increase in self-inhibition of PCC and inhibition from right amygdala is crucial for better regulation of negative emotions. Although, the self-reported negative emotion scores used in this experiment are not the direct measure of neuroticism, they may represent a trend towards trait-like personality related to negative emotions.

The results of current study showed strongest positive association of the self-connection of left amygdala with the high anger scores which is in line with the previously established connectivity of amygdala in anger circuitry (Richard et al., 2022). According to our results, the negative self-connection of left amygdala i.e., decrease in its inhibition is associated with the increase in anger-affect. Our results indicate positive association of PCC to left amygdala connectivity with low anger-affect while negative association of right amygdala to PCC connectivity with high anger-affect. Based on previous and the current study, amygdala is now regarded as a contributor to depression which reflect the state of sadness (Mouchet-Mages & Baylé, 2008). According to our results, low sadness has the strongest positive association with the (negative) self-connection of right amygdala and the strongest negative association with the (negative) self-connection of left amygdala. It reflects that decreasing the inhibition of right amygdala while increasing the inhibition of left amygdala may help regulate sadness. According to some previous work, the left amygdala is more closely associated with the encoding of affective information and has a stronger preference for language and feature extraction details (Frühholz et al., 2015; Nakamura et al., 2020), whereas the right amygdala has a stronger preference for retrieving visual affective information (Markowitsch, 1998). As a result, when compared to the left amygdala, the right amygdala may be concerned with a quicker but superficial interpretation of emotional stimuli.

There is already a well-established relationship between emotions and memory. The negative emotions are an outcome of self-referential and self-generated thoughts that are usually based on prior experience (Perkins et al., 2015). These thoughts are particularly significant in situations where declarative or explicit memory (episodic and/or semantic) is required to make sense of the environment. In the current study, the participant makes a conscious effort to recall memories that occurred during the last week for self-reporting of the negative emotions, hence the role of hippocampus is significant in our association results. The hippocampus has critical role in episodic memory (Burgess et al., 2002; Ezzati et al., 2016; Vargha-Khadem et al., 1997) with the differential association of left and right hippocampi in verbal memory (Frisk & Milner, 1990) and visual-spatial memory (Smith & Milner, 1981; Zammit et al., 2017) respectively. Previous research revealed the effect of emotions and neuropsychiatric disorders on the verbal episodic memory (Airaksinen et al., 2007; Heckers et al., 1998; Riegel et al., 2016). The verbal memory is more influenced by emotional speech, specifically negative emotions, than the neutral speech (Kensinger & Corkin, 2003; Schirmer et al., 2013) with enhanced activity in the left hippocampus (Maratos et al., 2001). According to our results, the (negative) self-connection of left hippocampus is negatively associated with low and high anger-affect and high sadness scores. Also, the average effective connectivity of (negative) self-connection of left hippocampus in high scores of all three emotions reflects that it is more sensitive to inputs from other brain regions in high negative emotions. This shows the potential significance of verbal episodic memory in negative emotions. In our findings, the high and low fear-affect had the strongest positive and strongest negative association with the (negative) self-connection of the right hippocampus respectively. The critical involvement of hippocampus in spatial memory, subsequently, in the encoding and storage of contextual fear information is already established through the previous literature (de Voogd et al., 2020; Wiltgen et al., 2006) Hence, our results may suggest the importance of right hippocampus for the fear-affect with reference to the spatial memory mapping.

The other crucial brain regions associated with emotion processing are the insular cortex and dACC. Particularly, being hub of the salience network, anterior insula has been suggested to be essential for interoceptive awareness and emotion processing (Gu et al., 2013; Park & Tallon-Baudry, 2014). The left anterior insula has significant role in the interoception (Craig, 2002) and subjective feelings (Craig, 2009). The anterior insula may also be a crucial junction for combining bottom-up information regarding interoceptive experiences with top-down regulatory signals (Gu et al., 2013). According to a meta-analysis, some voxels of left anterior insula show more activation in the state of anger than any other emotional state and right anterior insula activity was probably enhanced when participants were consciously assessing and expressing their feelings (Lindquist et al., 2012). This highlights our association results for low anger-affect and low fear-affect showing positive association with (negative) self-connection of rAI. These results suggest that the decrease in inhibition of rAI may be related to the conscious assessment of negative emotion. Low fear had the strongest positive association with the self-connection of rAI. Patients with major depressive disorder have consistently demonstrated lower insular activity (Fitzgerald et al., 2008). Our results also showed negative association of lAI to lHP connectivity with low sadness and the strongest negative association of lAI to rHP with low anger-affect. We also found the strongest positive association of dACC self-connection with high sadness and a positive association with high fear-affect. The dACC, being the key node of the salience network integrates information from the internal and external sources to guide the behavior. Besides amygdala, dACC is also an important part of the fear circuitry (Maier et al., 2012; Milad et al., 2007). Fearful experiences and threat appraisal heightened the activity of dACC (Lin et al., 2015; Maier et al., 2012). The identification of a neural mechanism that may underlie the sadness depends on understanding how various sub-regions of the anterior cingulate cortex affect the persistence of negative emotions (Schwartz et al., 2019).

Conclusion

Our findings revealed that the connectivity from right amygdala to PCC may be the main neural mechanism for high levels of self-reported negative emotions including anger, fear, and sadness. It may also represent the neural basis of trait-like personality related to negative emotions. Contrary to the previous literature, no causal connection was found between amygdala and medial prefrontal cortex. On the other hand, medial prefrontal cortex was influenced by hippocampus in high fear-affect and high sadness. The results of this study may be helpful for the comparative analysis of brain representations of mental health disorders.

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Figure legends

Figure 1. Association of effective connectivity and anger-affect (a) This panel shows the association of effective connectivity with self-reported low anger-affect scores (b) This panel shows the association of effective connectivity with self-reported high anger-affect scores. In both figures' matrices, positive values (green gradient) represent positive association while negative values (brown gradient) represent negative association between effective connectivity and anger-affect scores. Displayed values are the normalized beta coefficients representing the contribution of group-level parameter (anger-affect) with the effective connectivity. All values are the estimated parameters of the averaged model that passed the threshold of posterior probability > 0.95 (representing strong statistical evidence). The green and brown edges on the brain wiring diagram represent positive and negative associations respectively. Solid and dashed *extrinsic*, or between region, connections represent the association with excitatory and inhibitory effective connectivity respectively while solid and dashed *intrinsic* connections, within region or self-connections, represent the association with positive and negative self-connections respectively where self-connections are always inhibitory. Abbreviations: mPFC = medial prefrontal cortex, PCC = posterior cingulate cortex, HP = hippocampus, dACC = dorsal anterior cingulate cortex, AI = anterior insula, AMG = amygdala, DLPFC = dorsolateral prefrontal cortex

Figure 2. Association of effective connectivity and fear-affect (a) This panel shows the association of effective connectivity with low self-reported fear-affect scores (b) This panel shows the association of effective connectivity with high self-reported fear-affect scores. This figure follows the same color scheme and abbreviations as Figure 1. All values are the estimated

parameters of the averaged model that passed the threshold of posterior probability > 0.95 (representing strong statistical evidence).

Figure 3. Association of effective connectivity and sadness (a) This panel shows the association of effective connectivity with low self-reported sadness scores (b) This panel shows the association of effective connectivity with high sadness scores. This figure follows the same color scheme and abbreviations as Figure 1. All values are the estimated parameters of the averaged model that passed the threshold of posterior probability > 0.95 (representing strong statistical evidence).

Figure 4. Strongest positive and negative associations of effective connectivity with basic negative emotions Green and brown arrows show the strongest positive and negative associations respectively. Line annotations: LA = Low anger, HA = High anger, LF = Low fear, HF = High fear, LS = Low sadness, HS = High sadness. Abbreviations: mPFC = medial prefrontal cortex, PCC = posterior cingulate cortex, HP = hippocampus, dACC = dorsal anterior cingulate cortex, AI = anterior insula, AMG = amygdala, DLPFC = dorsolateral prefrontal cortex

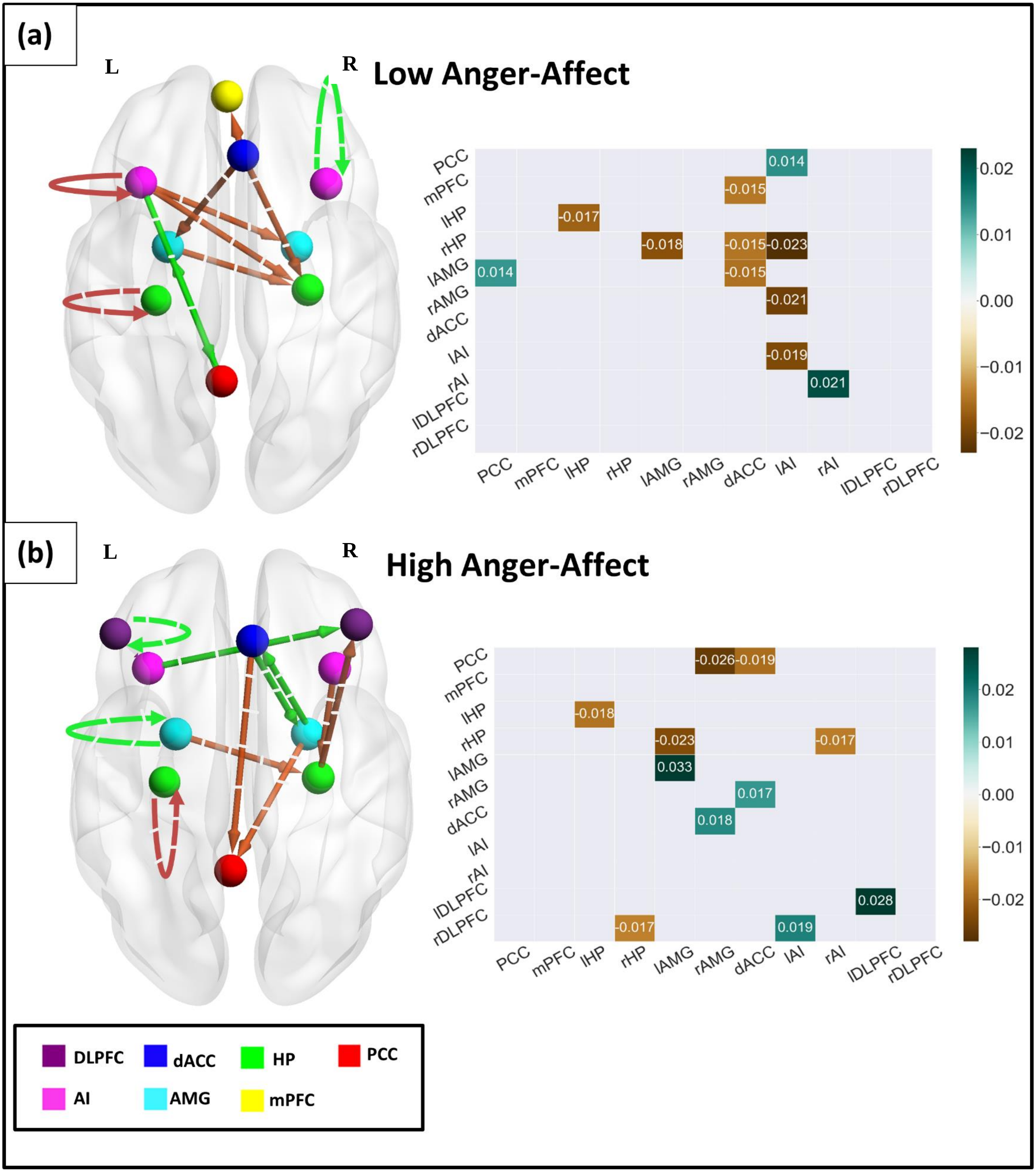

Figure 1. Association of effective connectivity with anger-affect

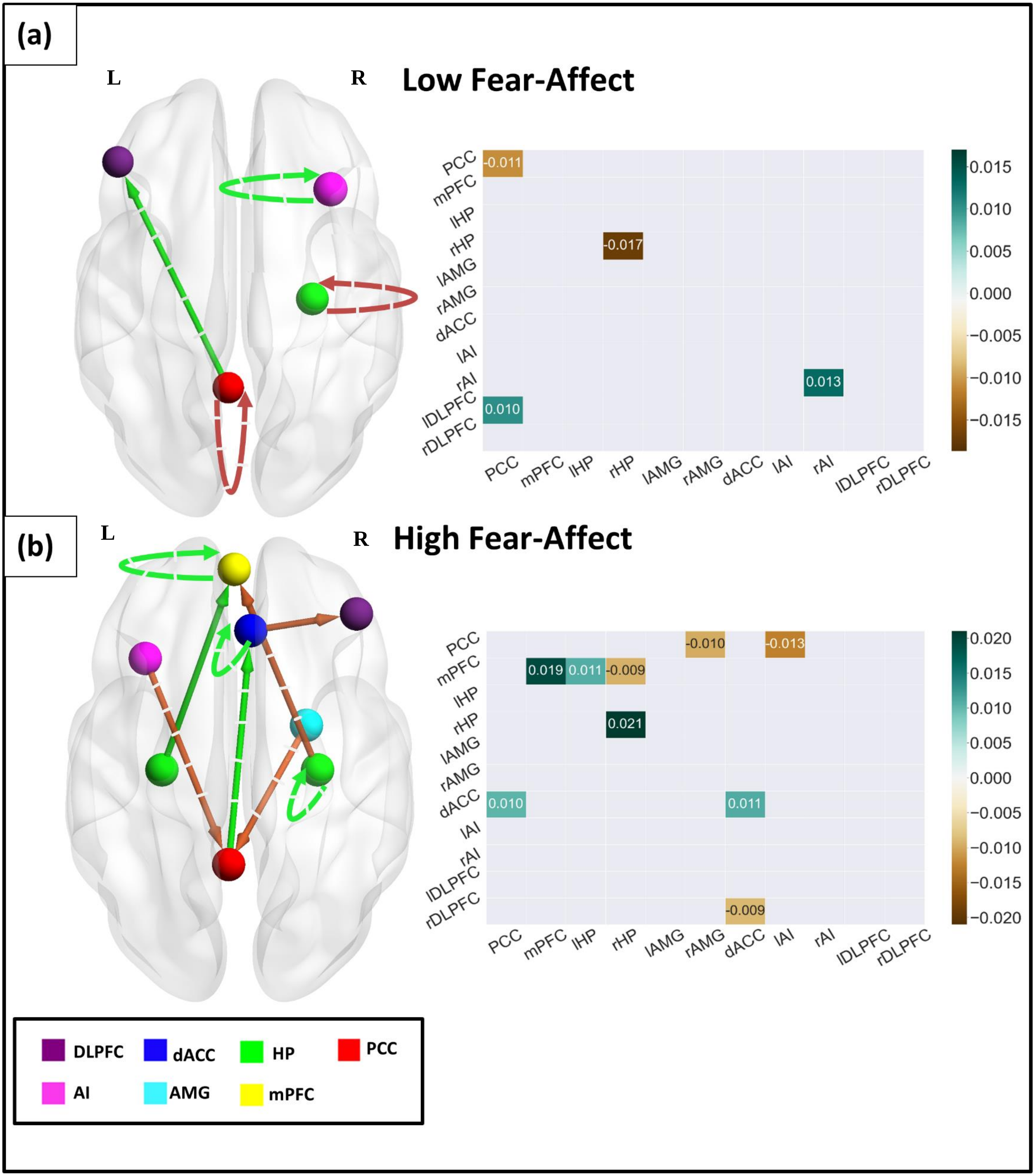

Figure 2. Association of effective connectivity with fear-affect

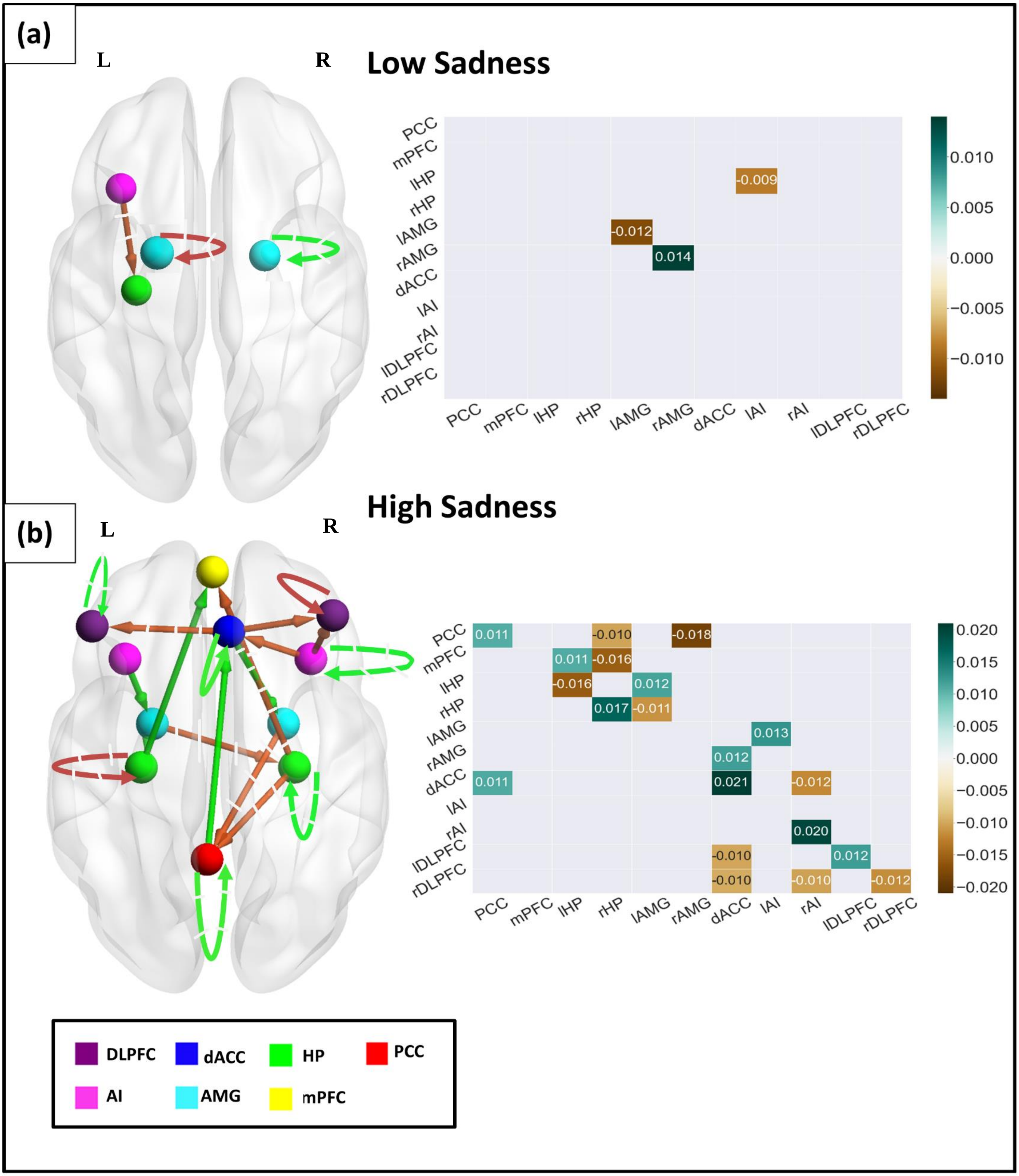

Figure 3. Association of effective connectivity with sadness

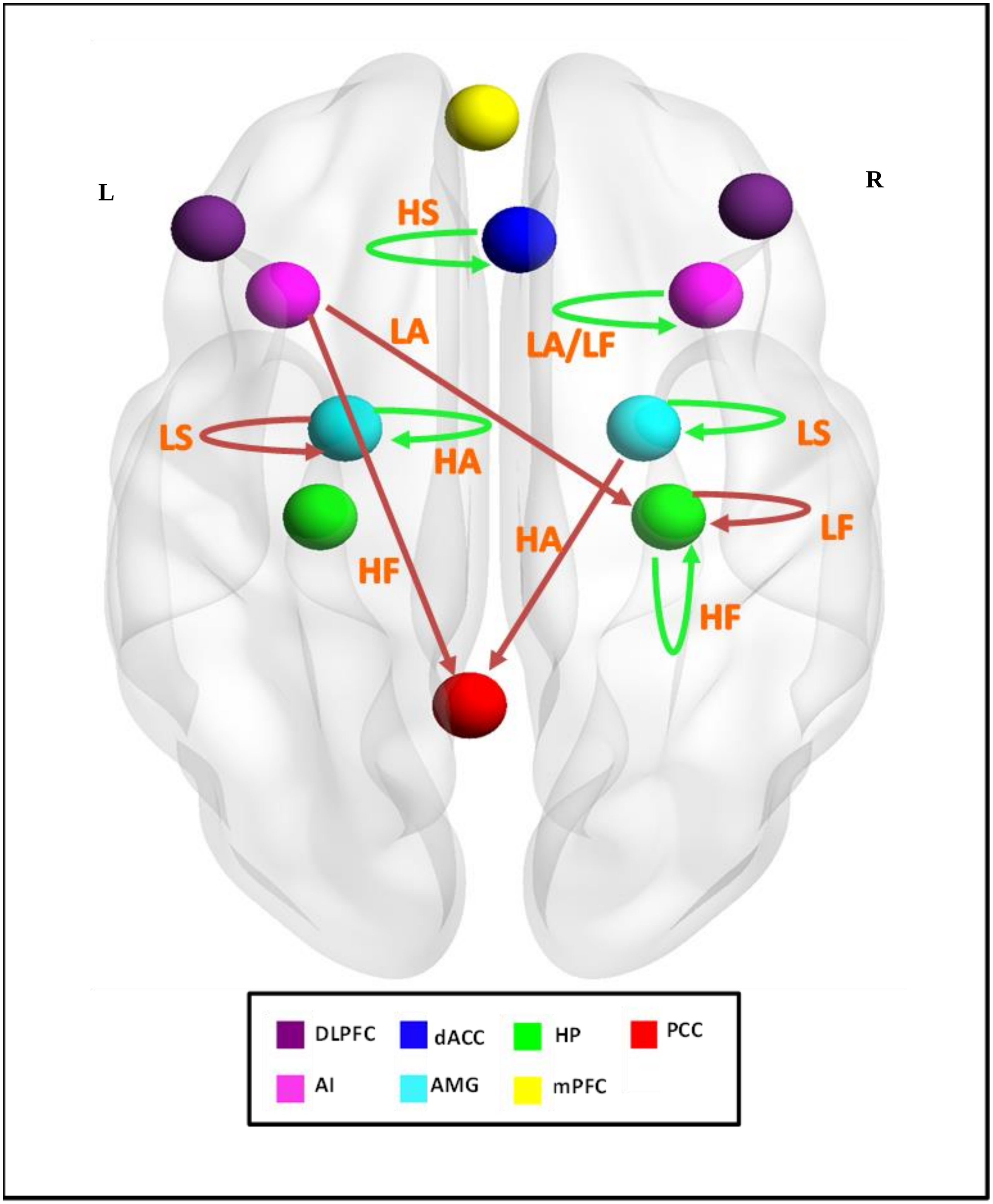

Figure 4. Strongest positive and negative associations of effective connectivity with basic negative emotions

Table 1. MNI Coordinates of ROIs centroids

ROI	**MNI Coordinates**
PCC	(-4, -52, 24)
mPFC	(-2, 54, 18)
lHP, rHP	(-28, -18, -16), (28, -18, -16)
lAMG, rAMG	(-24, -2, -22), (24, -2, -22)
dACC	(4, 32, 22)
lAI, rAI	(-34, 22, 0), (34, 22, 2)
lDLPFC, rDLPFC	(-46, 34, 32), (42, 38, 32)