Dynamic Causal Modeling of Effective Connectivity During Anger Experience in Healthy Young Men: 7T Magnetic Resonance Imaging Study

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KEYWORDS

anger processing;
dynamic causal modeling;
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film clip

ABSTRACT

Little is known about how anger-associated brain regions integrate and modulate external input. Therefore, we investigated the neural connectivity architecture of anger processing using a dynamic causal modeling (DCM) approach. Thirteen subjects underwent functional magnetic resonance imaging (fMRI) while viewing anger-inducing film clips. Conventional fMRI and DCM analyses were conducted to identify a dominant connectivity model. Viewing anger-inducing film clips led to activation in the left superior temporal gyrus, left insula, and left orbitofrontal cortex (OFC). The results of a group-level comparison of eight connectivity models based on conventional fMRI findings showed superiority of the model including reciprocal effective connectivities between the left insula, left superior temporal gyrus, and left orbitofrontal gyrus and bottom-up connectivity from the left superior temporal gyrus to the left orbitofrontal gyrus. Positive coupling effects were identified for connectivities between the left superior temporal gyrus and left insula and the left superior temporal gyrus and left OFC. A negative coupling effect was identified for connectivity between the left OFC and left insula. In conclusion, we propose a model of effective connectivity associated with the anger experience based on dynamic causal modeling. The findings have implications for various psychiatric disorders related to abnormalities in anger processing.

INTRODUCTION

Anger is an intense, uncomfortable emotional response to perceived provocation, insult, or offense (Videbeck, 2013). Anger contributes adaptively to survival by alerting an individual to potential or actual problems on an individual, interpersonal, or societal scale; however, uncontrolled anger can lead to negative effects on personal or social well-being (Novaco, 1976). Neuroscientists as well as social, clinical, and personality psychologists are deeply interested in understanding the neural mechanisms of anger processing and the biological factors that predispose individuals to aggression (Denson, Pedersen, Ronquillo, & Nandy, 2009).

A number of neuroimaging studies have investigated the neural substrates of anger in healthy subjects (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012; Murphy, Nimmo-Smith, & Lawrence, 2003;

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Phan, Wager, Taylor, & Liberzon, 2002; Wager et al., 2008). Studies on anger processing can be classified as investigations of anger experience or of anger perception. Anger perception involves observation of and judgments about the normative content of a stimulus, such as whether a picture of a facial expression resembles anger, fear, or disgust. In contrast, anger experience refers to the generation of angry feelings in response to pictures, sounds, memories, or other stimuli (Lindquist et al., 2012). Until now, most studies on anger processing have examined anger perception using experimental paradigms such as the facial judgment task or facial matching task, rather than tasks that generate an anger experience. Effective connectivity within the cortical network has also been examined for anger perception (Bakke, 2012; Fairhall & Ishai, 2006). However, there have been very few such studies on anger processing including not only anger perception but also experience. Several meta-analyses of neuroimaging studies on emotion concluded that regions and patterns of brain activation differ across various emotional experiences and perceptions (Murphy et al., 2003; Phan et al., 2002; Wager et al., 2008). Therefore, to examine the effective connectivity of neural substrates related to overall anger processing, a paradigm including anger experience and perception should be used.

There are several established techniques for eliciting emotional processing, including exposure to emotional images, autobiographical recollection, mental imagery, and emotional film clips. Compared to other methods, exposure to an emotional film clip has several benefits (Schaefer, Nils, Sanchez, & Philippot, 2010), in that film clips can evoke vivid feelings and elicit strong subjective and physiological changes. Accordingly, we used film clips to identify overall anger processing including anger perception and anger experience in the study.

Previous research has suggested that anger processing is a complex interaction among perception, experience, and regulation, related to different areas of the brain (Lindquist et al., 2012; Murphy et al., 2003; Phan et al., 2002; Wager et al., 2008). Anger perception comprises processing of social signals, such as those derived from others' faces, voices, gestures, and contextual information that individuals use to interpret others' behaviors (Baldwin, 1992; McArthur & Baron, 1983). Among other brain regions, the superior temporal gyri (STGs) are mainly engaged when processing various social signals (Adolphs, 2003; Allison, Puce, & McCarthy, 2000; Paulus, Feinstein, Leland, & Simmons, 2005; Singer, Kiebel, Winston, Dolan, & Frith, 2004; Xu, Gannon, Emmorey, Smith, & Braun, 2009). The anger experience is related to viscerotropic sensory responses enabling the individual to be in a state of readiness to take specific action (Lampert et al., 2002; Lampert, 2016; Mostofsky, Penner, & Mittleman, 2014; Suls, 2013; Taggart & Lambiase, 2011). Some studies have suggested that the anterior insula plays a key role in brain-heart interactions by controlling the cardiovascular sympathetic response (Critchley, 2009; Nagai, Hoshide, & Kario, 2010; Oppenheimer, 2006). Recently, a neuroanatomical study suggested two main functions of the insula, including integrating bottom-up interoceptive signals with top-down predictions to produce a present awareness state and contributing descending predictions to visceral systems that provide a point of reference for autonomic reflexes (Gu, Hof, Friston, & Fan, 2013). Anger regulation includes directing behav-

ior to a target by integrating the impulse to express the anger and the need to suppress any aggressive behavior in the current circumstances. The orbitofrontal cortex (OFC) is known to participate in this process (Bechara, Damasio, & Damasio, 2000; Grafman et al., 1996; Lindquist et al., 2012). However, conventional functional imaging analyses (i.e., functional specialization) have not fully elucidated the organization of these areas or how they integrate and modulate incoming information. Recently, to examine the organization, interrelationship, and integrated performance of functionally-specialized areas, several approaches have been developed, including functional connectivity and effective connectivity (Friston, 1994; Friston, Harrison, & Penny, 2003; Horwitz, 2003). Functional connectivity measures the temporal correlation of activity between brain areas, whereas effective connectivity measures directed influences of a brain area on another. Thus, effective connectivity can provide information associated with the causal processes that operate in brain function. In this study, we used the dynamic causal modeling (DCM) method to identify effective connectivity.

The DCM is a method for the interpretation of functional neuroimaging data that was developed to estimate intrinsic coupling (task-independent interactions) within a set of regions and to determine how coupling is influenced by experimental factors (e.g., time or context) (Friston et al., 2003). The DCM approach is used to infer causal relationships from functional imaging data or to determine a model that can explain a set of empirical observations among a predefined causal model set of alternatives. To determine the best model, the combined neuronal and hemodynamic parameters of DCM are estimated from measured blood oxygen level-dependent (BOLD) signals using iterative Bayesian estimation (Friston et al., 2003; Stephan, Weiskopf, Drysdale, Robinson, & Friston, 2007).

Recently, using the DCM method, Mazzola et al. (2016) studied the dynamic interplay between the insula and the STG when the participants encountered situations involving anger and found that there is reciprocal connectivity between these areas. However, they focused on the neural network related to affect, not to cognition, during emotional processing. Studies on emotion processing have suggested that affect and cognition are mediated by separate but interacting systems in the brain (LeDoux, 1989; Lemerise & Arsenio, 2000; Murphy et al., 2003). Hence, in this study we extended the results of previous studies to investigate the connectivity pattern subserving communication between affective and cognitive systems during anger processing. That is, the aim of this study was to investigate the connectivity pattern among brain areas related to anger perception, experience, and regulation (i.e., the insula, STG, and OFC) during anger processing. Specifically, based on the previous study which found that the insula plays a key role in the integration of bottom-up and top-down emotion generation (Gu et al., 2013), we hypothesized that the insula may be a hub of emotion processing in connecting the STG and the OFC and that there would be negative effective connectivity between the OFC and insula. To this end, we used functional magnetic resonance imaging (fMRI) combined with the DCM approach to investigate the neuronal interactions of different brain regions associated with anger and to determine how these interactions are modulated by anger-evoking stimuli.

MATERIALS AND METHODS

Participants

Thirteen male subjects participated in the fMRI experiment (M_{age} = 24.2 ± 2.26 years; range = 21–27 years). We recruited only male subjects because emotionally-evocative visual stimuli can vary in their effects depending on sex and age. The exclusion criteria included a history of head injury, drug or alcohol abuse, and any significant psychiatric condition as assessed by the *Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders version IV* (First, Spitzer, & Gibbon, 2002). All subjects provided written informed consent for study participation after being fully informed about the experimental procedure. The experimental protocol was approved by the local institutional review board (P01-201602-11-002).

Film Stimuli

We searched for anger-inducing film clips from movies, drama, news, and documentaries in advance, and consequently, 20 clips were selected. Anger-evoking film clips conveyed stories regarding child abuse, mocking a person with disabilities, racism, unfair treatment, and bullying. We conducted a pilot experiment with 52 men using these clips. These men were shown 20 film clips for 90 s each, in a randomized order. As a result, the five clips with the highest group-average ratings of anger were chosen. Most participants (96.06 ± 4.75%) reported that they experienced anger watching these clips, and the intensity was 3.29 ± 1.19 on a 6-point Likert scale (from 0 = *not angry at all* to 5 = *extremely angry*). The film clips for the fMRI study included five neutral clips with nonaffective nature scenes and the five anger-evoking clips. The neutral clips were matched in terms of color and hue.

Experimental Paradigm and Procedure

The fMRI task comprised two conditions: a neutral condition and an anger-inducing condition. Each condition was composed of five 30 s blocks. A 12 s interstimulus interval preceded each block. Each block was presented randomly to eliminate order effects. The total scanning session required approximately 7 min (see Figure 1).

Self-Report of Subjective Anger

After completing the fMRI scanning, the participants watched the same film clips that were shown during the fMRI scanning, and they were instructed to respond to the following questions in order to evaluate suitability and effectiveness. At first, they were required to answer whether anger was evoked while watching the film clips. Second, they were asked to evaluate the anger intensity of each film clip on a scale from 0 to 5 (0 = *not angry at all* to 5 = *extremely angry*) and to indicate the sections that evoked the most intense emotions. Finally, they were required to report any emotions (i.e., sadness, happiness, fear, disgust, surprise) that they may have experienced other than anger during their exposure to each film clip.

fMRI Acquisition

Imaging was performed using a 7.0-T Philips Achieva MR scanner equipped with a 32-channel NOVA head coil. The parameters for scanning were as follows: repetition time (TR) = 2000 ms; echo time (TE) = 17 ms; flip angle = 70 °; field of view = 192 × 198 × 72 mm³; matrix = 128 × 129; slice thickness = 3 mm; and in-plane resolution = 1.5 × 1.5 × 3 mm³. T1-weighted anatomical images were obtained using a 3D fast field echo sequence with the following parameters: TR = 5.5 s; TE = 2.6 ms; flip angle = 7 °; field of view = 234 × 234 mm²; voxel size = 0.67 × 0.67 × 0.67 mm³.

Analysis of fMRI Processing

To induce emotions more vividly, we used film clips, not pictures or scripts, in this study. However, some researchers have contested that film clips may elicit "blends" of emotions rather than "pure" ones (Hemenover & Schimmack, 2007; Larsen, McGraw, & Cacioppo, 2001; Schimmack, 2001). To solve this problem, we excluded the data obtained from those clips that did not evoke anger or induced emotions other than anger from the analysis.

The first three image volumes were discarded to avoid instability of the initial MRI signal. Thereafter, functional data were processed using the statistical parametric mapping program SPM 12 (www.fil.ion.ucl.ac.uk/spm). The images were corrected for slice acquisition timing and then realigned to the first functional image. Anatomical
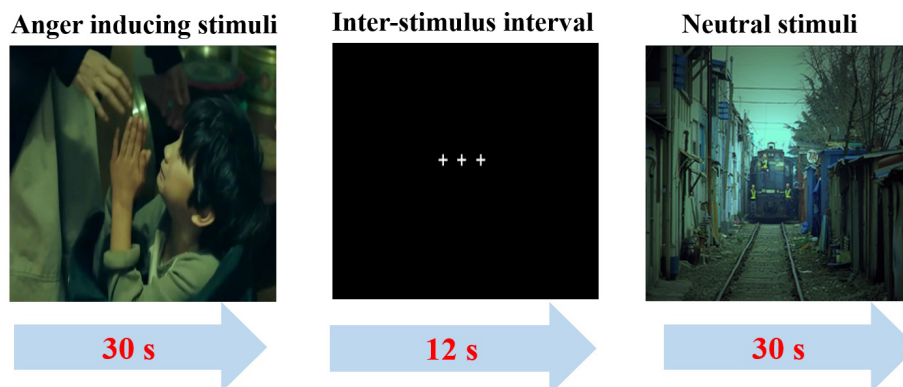
Anger inducing stimuli **Inter-stimulus interval** **Neutral stimuli**

30 s   **12 s**   **30 s**

FIGURE 1.

The experimental paradigm for the fMRI imaging.

images were coregistered to the mean echo-planar image, and the coregistered images were subsequently normalized into the standard Montreal Neurological Institute (MNI) template. Normalized images were smoothed with an 8 mm Gaussian kernel. A design matrix modeling the anger-evoking and neutral conditions was constructed for each subject. A contrast was performed for each subject to identify anger-specific neural substrates, using t-tests to compare the anger-evoking and neutral conditions. The results were input to a random effects analysis of group inferences. Activations were considered significant at $p < .05$ (family-wise error [FWE]-corrected at voxel-level) with a minimum cluster size of $k = 10$. The brain coordinates in the fMRI results were extracted according to the MNI coordinate system, which is the template used for SPM. Finally, the MNI coordinates were converted to Talairach space using the Talairach Software (University of Texas Health Science Center, San Antonio, TX).

Analysis of DCM Processing

We used the DCM technique in the SPM 12 toolbox to identify mutual influences among the neural substrates involved in anger processing (Friston et al., 2003). Specifically, the DCM enabled us to identify regional effects in terms of changing patterns of connectivity among the areas in relation to the experimentally-induced contextual modulation of connection strengths among the regions of interest (ROIs, Mazzola et al., 2016). Based on the findings of previous neuroimaging studies on anger processing and the results of the conventional analysis, three ROIs were defined in the following regions: the left anterior insula, the left STG, and the left OFC (see Table 1, Lindquist et al., 2012; Murphy et al., 2003; Phan et al., 2002; Wager et al., 2008). The BOLD time series data were extracted as the first eigenvariates of all significant voxels within a 5 mm radius sphere centered on each participant's local maxima in each ROI, as obtained from the results of the group analysis (anger-evoking condition vs. neutral condition).

Our DCM design matrices included regressor modeling of the effect of anger (anger-evoking condition) among the three regions including the insula, the STG, and the OFC. We created a subset of eight models based on our results and those of previous studies (see Figure 3, Deen, Pitskel, & Pelphrey, 2010; Mazzola et al., 2016; Mesulam & Mufson, 1982). In each subject, a DCM was specified with bidirectional and intrinsic connectivity among the three regions. Tract-tracing and resting-state fMRI have shown that the anterior insula has reciprocal connections with superior temporal areas and the OFC; these areas comprise the insulo-orbito-temporal network in the paralimbic brain (Deen et al., 2010; Mazzola et al., 2016). Recently, a study on the functional connectivity between the STG and the insula during anger processing also supported is the existence of a reciprocal connectivity between these areas. Therefore, in all models for the study, the left insula had bidirectional connections with the STG, corresponding to anatomical and functional evidence for connections between the two areas (Deen et al., 2010; Mazzola et al., 2016; Mesulam & Mufson, 1982). Yet, functional connectivities between the insula - OFC and the STG - OFC during anger processing were not found. Eight model variants were then produced by setting an information conductance

pattern, involving factors such as connectivity (parallel, serial, or full) and directionality (unidirectional or bidirectional) between the insula - OFC and the STG - OFC. In all models, the left STG received all anger-inducing conditions as a driving input.

After estimation, model comparison was implemented using random-effects Bayesian model selection (BMS) to compute exceedance and posterior probabilities at the group level (Kasess et al., 2010; Penny, Stephan, Mechelli, & Friston, 2004; Stephan, Penny, Daunizeau, Moran, & Friston, 2009). A Bayesian model average (BMA) analysis was then performed to infer the model structure (i.e., the significant connections between the ROIs) and the connectivity parameters among the groups. These values were entered to the within-group analysis for individual connections using one sample t-tests with false discovery rate (FDR) correction.

RESULTS

Subject Reporting

The concordance rate (positive anger responses to anger-evoking films) of the pictures presented was 74 ± 8.40%. The average intensity of anger induced by anger-evoking films, rated on a 6-point scale, was 3.86 ± 0.72 points.

Conventional fMRI Analysis

To examine brain areas specifically related to anger processing, BOLD responses were contrasted between the anger-evoking and neutral conditions. Enhanced activation was observed in the bilateral middle occipital gyrus (Brodmann areas [BAs] 18 and 19), fusiform gyrus (BA 37), left OFC (BA 47), bilateral anterior temporal cortex, left insula, bilateral globus pallidus, left thalamus, and amygdala in the anger-evoking compared to the neutral condition (FWE-corrected $p < .05$ at voxel-level with a minimum cluster size of $k = 10$; see Table 1 and Figure 2). No region exhibited a higher BOLD signal in the neutral condition than in the anger-evoking condition.

TABLE 1.

Coordinates and t Scores for the Activated Areas

L/R	Region	Talairach coordinates			t value
		X	Y	Z	
L	Middle occipital gyrus	−30	−92	−2	5.44
		25	−75	−2	5.28
L/R	Fusiform gyrus	−50	−58	−20	5.31
		48	−50	−16	5.68
L	Orbitofrontal cortex	−48	36	−4	6.75*
L/R	Superior temporal cortex	−62	−20	2	6.49*
		64	2	−6	6.20
L	Insula	−32	16	12	6.73*
L/R	Putamen	−22	10	−6	5.77
		15	−7	2	5.49
L	Thalamus	−19	−19	14	5.12
L	Amygdala	−17	−6	−9	4.99

Note. L = left; R = right; * = the peaks used for the dynamic causal modeling with an asterisk. Anger condition > Neutral condition; $p < .05$, corrected for Family-wise error rate at at voxel-level with a minimum cluster size of $k = 10$
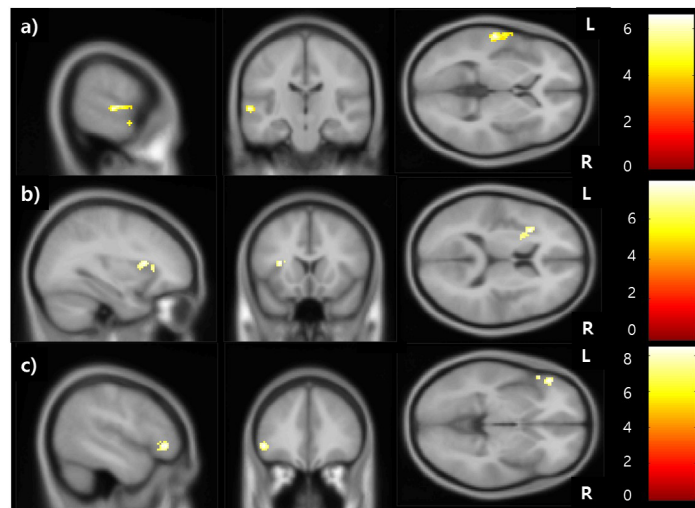
FIGURE 2.

Regions of interest for the dynamic causal models. Panel A: Left superior temporal gyrus (X, Y, Z coordinates: -62, -20, 2). Panel B: Left insula (-32, 16, 12). Panel C: Left orbitofrontal cortex (-48, 36, -4). Maps were thresholded at $p < .05$ (family-wise error rate-corrected at voxel-level) with a minimum cluster size of $k = 10$.
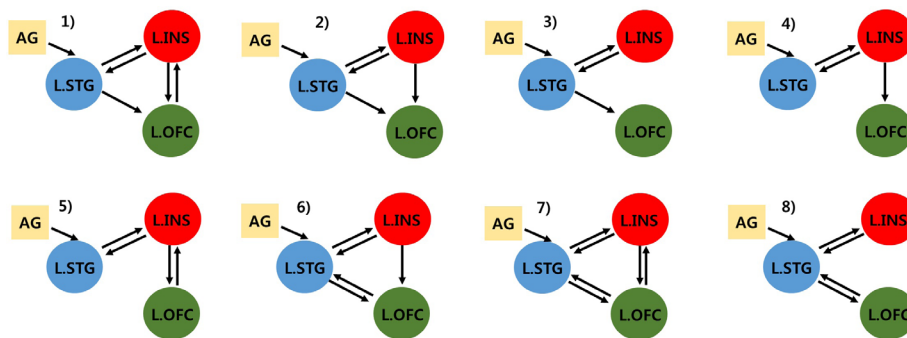

FIGURE 3.

Subset of eight models for the dynamic causal modeling analysis. AG = anger influence; L. INS = left insula; L. OFC = left orbitofrontal cortex; L. STG = left superior temporal gyrus.
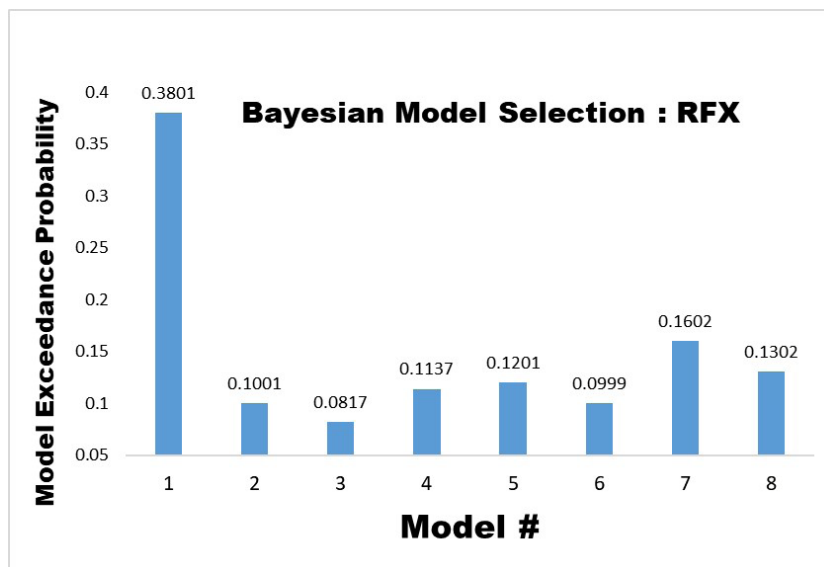

FIGURE 4.

The results of Bayesian model selection.

Dynamic Causal Modeling Analysis

We identified effective connectivity among the left anterior insula, left OFC, and left STG by modeling the extracted time course using DCM (see Table 1). Figure 4 shows the results of comparisons among eight dynamic causal models using BMS. With the Bayesian approach, it is commonly presumed that the optimal predictive model is the model with the highest posterior probability (Barbieri & Berger, 2004). In group BMS, Model 1 was optimal, with the highest posterior probability (38.01%). This winning model consisted of reciprocal effective connectivities between the left insula and the left STG as well as the left OFC, and also included bottom-up connectivity from the left STG to the left OFC.

To determine parameter estimates among the regions of Model 1, effective connectivity strengths of neuronal coupling were calculated using the BMA. Table 2 summarizes the BMA results and effective connectivities among the ROIs across all subjects and models (Corrected FDR at $p < .05$). Figure 5 shows a compatible architecture specifying intrinsic connections during anger processing. The solid and thick solid lines define significant ($p < .05$), and very significant ($p < .01$; $p < .001$) connections, respectively. The intrinsic coupling parameters shown in the figure represent the endogenous coupling strengths between source areas and targets corresponding to frequencies in Hz. The coupling strength was strongest between the left STG and the left insula. A positive parameter indicates an enhancing influence of the origin region on the target region, whereas a negative parameter indicates that an increase in activity in the source region results in decreased activity in the target region (Mechelli, Price, Noppeney, & Friston, 2003). That is, increased activity in the left STG led to increased activity in the left insula and left OFC. Activation of the left insula also enhanced activation of the STG. In contrast, increased activity in the left OFC (or left insula) diminished activity in the left insula (and left OFC).

DISCUSSION

In the present study, we expand on previous evidence from recently published studies on anger processing (Lindquist et al., 2012; Murphy et al., 2003; Phan et al., 2002; Wager et al., 2008). We identified a neural network subserving the processing of anger that includes connectivity between the left insula, left STG, and left OFC, as well as bottom-up connectivity between the left STG and left OFC.

The results of our conventional analysis are consistent with the findings of previous neuroimaging studies on anger processing (Lindquist et al., 2012; Murphy et al., 2003; Phan et al., 2002; Wager et al., 2008); we identified activity related to the experience of anger in various areas including the fusiform gyrus, amygdala, putamen, OFC, anterior insula, and STG. These regions are known to be related to emotion processing functions such as facial recognition, emotional perception, experience, regulation, and reaction (Adolphs, 2002). The bilateral middle occipital lobe including the fusiform gyrus is reportedly linked to the recognition and determination of a stimulus as emotional. According to previous studies on the emotions induced by visual stimuli, the occipital lobe including the fusiform gyrus is activated to a greater extent when emotional rather than nonemotional visual stimuli are presented, due to increased attention (Corbetta, Miezin, Dobmeyer, Shulman, & Petersen, 1991; Lane, Reiman, Ahern, Schwartz, & Davidson, 1997; Lane, Reiman, Bradley et al., 1997). Evidence from animal studies (Maeda, Morimoto, & Yanagimoto, 1993; Ono & Nishijo, 1992), lesion studies (Aggleton & Young, 2000), and neuroimaging studies (Morris, Öhman, & Dolan, 1998; Whalen et al., 1998) has suggested that the amygdala is not involved in the perception of basic sensory stimuli but in the subliminal perception of emotional stimuli, which specifically includes the decoding of emotional reactions corresponding to their significance. The putamen is one of the structures that comprises the basal ganglia, and it is known to be associated with motor control, cognition, emotion, and somatosensory functions (Arsalidou, Duerden, & Taylor, 2013). According to previous studies, the putamen is associated with the recognition of emotional facial expressions (Calder, Keane, Manes, Antoun, & Young, 2000, Calder, Keane, Lawrence, & Manes, 2004; Phillips et al., 1998). Among the activated regions, the STG, anterior insula, and OFC are thought to be functionally specialized for the processing of anger. Based on our study findings and the known roles of these areas, we speculate that anger processing involves interactions among the left insula, left STG, and left OFC.

We used the DCM to determine intrinsic connections between our target areas and identified strong endogenous connectivity between the left STG and left insula across all subjects. This result reaffirmed a previously reported parallel pattern of connectivity between the STG and insula for the recognition and processing of angry faces (Mazzola et al., 2016).

Numerous noninvasive brain stimulation and neuroimaging studies have investigated the functions of the STG. These studies have con-

TABLE 2.

Estimated Coupling Parameters Among Regions of Interest

Areas		Mean	SD	Maximum	Minimum	Median	p value
Origin	Target						
Superior temporal gyrus	Anterior insula	0.32	0.13	0.67	0.13	0.31	< .001
Anterior insula	Superior temporal gyrus	0.17	0.06	0.28	0.04	0.16	< .01
Superior temporal gyrus	Orbitofrontal gyrus	0.13	0.09	0.27	−0.02	0.13	< .05
Anterior insula	Orbitofrontal gyrus	−0.05	0.05	0.04	−0.15	−0.04	< .001
Orbitofrontal gyrus	Anterior insula	−0.07	0.05	−0.01	−0.16	−0.06	< .001

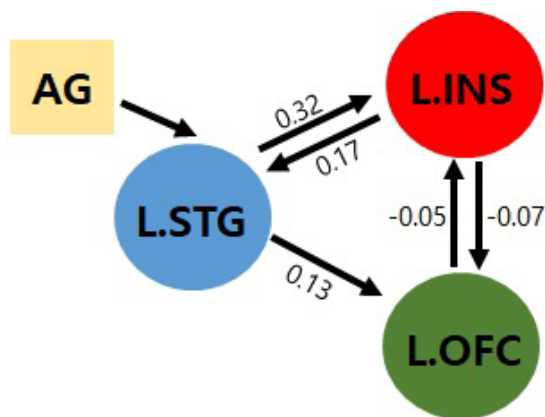*Note.* Difference significant at $p < .05$ (Bonferroni corrected for multiple comparisons).

FIGURE 5.
Connectivity strength of the winning model.

sistently associated task-related STG activation with anger processing (Frühholz & Grandjean, 2012; Mazzola et al., 2016; Sander et al., 2005). Activation in the STG was reported during decoding of angry vocal expressions, angry voice prosody processing (Frühholz & Grandjean, 2012; Sander et al., 2005), and anger-inducing situations (Allison et al., 2000; Xu et al., 2009). The STG is involved in processing a diverse array of socially-salient stimuli, such as those derived from other individuals' faces, voices, gestures, and contextual information (Allison et al., 2000; Mazzola et al., 2016; Mechelli et al., 2003; Singer et al., 2004; Xu et al., 2009). Other neuroimaging evidence suggests that dysfunction of the STG plays a role in psychiatric disorders involving impairment of social cognition and social functioning, such as autism spectrum disorder and schizophrenia (Cheng, Rolls, Gu, Zhang, & Feng, 2015; Green, & Leitman, 2008; Mazzola et al, 2016).

The anterior insula is thought to be involved in the awareness of bodily sensations, interoception, and the awareness of affective feelings (Adolphs, 2002; Craig, 2009). Bodily sensations can be experienced as states with some level of emotional arousal. A previous meta-analysis determined that activation of the left anterior insula was consistently increased during the experience of anger, compared to any other emotional category (Lindquist et al., 2012). A human neuroimaging study using diffusion tensor imaging found that the anterior insula is interconnected to regions of the OFC (Craig, 2009). Consistent with this study, we identified functional connectivity between the left insula and the OFC. Additionally, the left insula and the OFC exhibited inverse patterns of activation; this result partially supports the findings of a previous study on connectivity between the OFC and the insula during high-level threat processing (Barbas, 1995; Lim, Padmala, & Pessoa, 2008; Pessoa, 2009). Although the OFC is a large structure that is undoubtedly associated with other psychological phenomena, previous meta-analyses of neuroimaging literature have proposed a primary role for the OFC in anger (Lindquist et al., 2012; Murphy et al., 2003; Vytal & Hamann, 2010). The OFC influences affect by integrating exteroceptive (information from the world) and interoceptive (information from the body) sensations to guide behavior (Lindquist et al., 2012), such that individuals with damage to the OFC exhibit an inability to integrate exteroceptive and interoceptive sensory information, resulting in

inappropriate behavior and aggression (Bechara et al., 2000; Grafman et al., 1996). Indeed, individuals with psychopathy traits and antisocial personality disorder featuring increased aggression show changes in the function and structure of the OFC (Glenn & Raine, 2009; Harenski, Kim, & Hamann, 2009; Raine, 2002; Yang & Raine, 2009). Taken together, these findings and our results support a clear role for the OFC in anger as a center for the integration of multimodal sensations.

One of the most interesting findings was a dominant model including one positive reciprocal connectivity (i.e., insula - STG) and one negative reciprocal connectivity (i.e., insula - OFC). The results showed that mutual inhibition between elaborative processing (in the left OFC) and affective awareness (in the left insula) is involved in emotional processing. Electroencephalographic (Harmon-Jones & Allen, 1998; Harmon-Jones & Sigelman, 2001) and functional neuroimaging (Blair, Morris, Frith, Perrett, & Dolan, 1999; Damasio et al., 2000; Dougherty et al., 1999; Kimbrell et al., 1999; Pietrini, Guazzelli, Basso, Jaffe, & Grafman, 2000) studies have used emotion induction paradigms to examine the neural substrates associated with anger in healthy subjects. Although these studies used different techniques to induce anger, all have revealed the involvement of common anterior paralimbic structures for emotional experiences together with the prefrontal cortex (PFC), including the OFC for cognitive processing, during anger states. This finding showed that several regions of the PFC, including the OFC, play a crucial role in constraining impulsive outbursts (Davidson, Putnam, & Larson, 2000; Goldin, McRae, Ramel, & Gross 2008). Thus, it is proposed that cognitive processing and emotional experiences are separated in anger processing. The negative reciprocal connectivity (i.e., insula - OFC) revealed in the current study is also consistent with the general understanding about the role of the OFC in cognitive control of negative emotion.

Understanding effective connectivity during anger processing may advance investigations in patients with violent outbursts and aggressive acts, including those with intermittent explosive disorder and borderline personality disorder. Recently, Lee et al. (2016) found a subtle disruption of the long-range white matter tracks connecting the parietal and temporal lobes to the frontal cortex in intermittent explosive disorder patients. This result provides the first evidence of altered brain connectivity in people with anger-related disorders. However, they only showed a difference in anatomical connectivity, not in functional connectivity during the actual experience of anger. Hence, our effective connectivity model could be applied to identify functional dysconnectivity among such patients.

The present study has some limitations. First, our study does not address known sex differences in brain engagement during threat evaluation and the emotional perception of anger (McClure et al., 2004; Sabatinelli, Flaisch, Bradley, Fitzsimmons, & Lang, 2004), as we only included male subjects. Second, we cannot exclude the possible confounding effects of other factors such as motivation and cognition on our results. Thus, some ROIs activated in our study may have roles more directly related to motivation and cognition than to anger. Third, some brain areas known to play an important role in anger (i.e., the amygdala and putamen) were excluded from the DCM analysis.

Previous neuroimaging studies have suggested the specificity of these areas for negative emotion, including fear and anger. We also found activation in these areas during anger processing in the within-group analyses. However, the activation found in the group analysis does not signify that these areas were activated in each participant. To construct the individual model for the DCM analysis, the brain areas that are activated over a threshold should be included, with the threshold usually being determined by a researcher. Some participants did not show significant activation in the amygdala at a lower statistical threshold ($p < .001$, uncorrected). For this reason, the amygdala was excluded from the analysis in our study. Fourth, in previous studies, the right insula appeared to have a dominant role in emotional processing. However, in a recent study using quantitative meta-analytic methods, emotional stimuli predominantly activated the left anterior insula in men, whereas the bilateral anterior insula was activated in women (Duerden, Arsalidou, Lee, & Taylor, 2013). In this study, only the left insula was activated, possibly because we only included male participants. However, there is debate regarding the lateralization of affective processing in the insula. In further studies, we would like to consider this lateralization by examining other factors such as sex. Finally, to remove any confounding effects, we attempted to render the two types of film clips as similar as possible (i.e., in color and hue). However, due to their emotional characteristics, the levels of arousal and valence were not matched. Hence, the differences in brain responses between the two types of clips might be attributable not only to differences in elicited emotions (i.e., anger stimuli vs. neutral stimuli), but also to arousal and valence.

Even so, it is noteworthy that our results are consistent with those of previous studies on anger processing indicating important roles for the insula, STG, and OFC. Furthermore, the results have various implications by providing evidence that anger processing is modulated by affective awareness and cognitive regulation based on different couplings between the insula - STG and the insula - OFC. The results suggest that anger processing may depend on a more direct interaction between a system related to the regulation of emotion (i.e., the OFC) and a system associated with generating anger (i.e., the insula).

CONCLUSION

We have created a dynamic causal model to identify how the brain areas associated with emotional processing (i.e., emotional perception, experience, and regulation) mediate each other during anger processing. Our results should facilitate future investigations of anger processing in various psychiatric disorders, such as borderline personality disorder and intermittent explosive disorder, which are accompanied by abnormalities in emotional perception and regulation.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

AUTHORS' CONTRIBUTIONS

JWS made substantial contributions to conception and design, acquisition of the data, and analysis and interpretation of the data. JWS and CC were involved in drafting the manuscript and revising it critically for important intellectual content. All authors gave final approval of the version to be published.

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