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Interhemispheric Dorsolateral Prefrontal Cortex Connectivity is Associated with Individual Differences in Pain Sensitivity in Healthy Controls

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Abstract

The dorsolateral prefrontal cortex (DLPFC) is implicated in pain modulation through multiple psychological processes. Recent noninvasive brain stimulation studies suggest that interhemispheric DLPFC connectivity influences pain tolerance and discomfort by altering interhemispheric inhibition. The structure and role of interhemispheric DLPFC connectivity in pain processing have not been investigated. The present study used dynamic causal modeling (DCM) for fMRI to investigate transcallosal DLPFC connectivity during painful stimulation in healthy volunteers. DCM parameters were used to predict individual differences in sensitivity to noxious heat stimuli. Bayesian model selection results indicated that influences among the right DLPFC (rDLPFC) and left DLPFC (lDLPFC) are modulated during painful stimuli. Regression analyses revealed that greater rDLPFC → lDLPFC couplings were associated with higher suprathreshold pain temperatures. These results highlight the role of interhemispheric connectivity in pain modulation and support the preferential role of the right hemisphere in pain processing. Knowledge of these mechanisms may improve understanding of abnormal pain modulation in chronic pain populations.

Key words: DLPFC; effective connectivity; fMRI; interhemispheric; neuroimaging; pain processing

Introduction

The dorsolateral prefrontal cortex (DLPFC) is known to play a crucial role in multiple pain-related neural processes. Specifically, the DLPFC has been implicated in endogenous pain modulation and analgesia through numerous cognitive and emotional processes such as attention, anticipation, reappraisal, expectation, placebo analgesia, and desire for relief (Benedetti et al., 2005; Bushnell et al., 2013; Craggs et al., 2007; Kong et al., 2013; Lorenz et al., 2003; Stein et al., 2012; Tracey and Mantyh, 2007; Wager et al., 2004; Wiech et al., 2008). The DLPFC may also be impacted by chronic pain conditions, which are associated with decreased prefrontal cortex gray matter density (Apkarian et al., 2011).

Findings from neuroimaging studies of psychological processes and psychiatric conditions suggest that elucidation of interhemispheric connectivity in pain processing will likely further our understanding of the neural mechanisms involved (Anderson et al., 2011; Bloom and Hynd, 2005; Hofman and Schutter, 2009; Rüsch et al., 2010; Stephan et al., 2007; Thiruvady et al., 2007; Voineskos et al., 2010; Xu et al., 2013). Likewise, Kaller et al. (2015), indicated that structural, transcallosal DLPFC pathways appear to maintain hemispheric functional asymmetries. These authors also found that individual differences in DLPFC–DLPFC structural connectivity relate to differences in cognitive processing. Although current literature has documented many aspects of DLPFC connectivity with other brain regions in pain processing, the role of interhemispheric DLPFC connectivity has received little attention.

Recently, the DLPFC has been a site of manipulation in noninvasive brain stimulation studies. Investigations utilizing transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) provided initial evidence that DLPFC stimulation may have a role in decreasing pain reports (Boggio et al., 2009; Borckardt et al., 2006; Brighina et al., 2011) and increasing pain tolerance (Borckardt et al., 2007; Lefaucheur et al., 2008; Mylius et al., 2012). A potential mechanism for some of these findings is the modulation of DLPFC interhemispheric connectivity (interactions among the left DLPFC (lDLPFC) and right DLPFC (rDLPFC) across the corpus callosum). Graff-Guerrero et al. (2005) found that low-frequency

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rTMS, which is thought to have inhibitory effects, applied to the rDLPFC resulted in increased pain tolerance. Citing evidence in support of increased right-hemisphere lateralization of pain processing, they hypothesized that right hemisphere suppression resulted in the removal of transcallosal inhibition, thereby allowing increased descending inhibition from the left hemisphere. Despite these promising findings, the neural mechanisms underlying these changes remain poorly understood and improved mechanistic understanding is needed to further develop these modalities (Cheng, 2013).

To better understand the bihemispheric roles of the DLPFC in pain processing, further studies are needed. Currently, there are no studies that have characterized the role of DLPFC–DLPFC transcallosal connections in normal pain processing. The present study aims to clarify the structure and sensitivity of interhemispheric DLPFC effective connectivity during painful stimuli and determine its association with individual pain sensitivity. As such, the present study used dynamic causal modeling (DCM) to investigate directed regional influences among the lDLPFC and rDLPFC during painful thermal stimulation. We hypothesized that the strength of interhemispheric connectivity would be enhanced during painful stimuli and that the strength of pain-related connectivity modulation will be associated with decreased pain sensitivity.

Materials and Methods

The present analysis is a supplement to an NIH-funded fMRI investigation of the neural mechanisms involved in placebo analgesia (Sevel et al., 2015a, 2015b). Suprathreshold thermal pain temperatures were individually determined using visual analog scale (VAS) responses to thermal quantitative sensory testing (QST) during a screening visit. Individuals then completed one baseline fMRI visit, in which only thermal ''pain'' temperatures were applied, with no placebo conditioning or other manipulation. Data included in the present analyses were collected only during the baseline visit and represent brain activity associated with thermal, experimental pain. Methods described below represent procedures used for the baseline visit.

Participants

Data from 35 healthy individuals were analyzed in this study (mean age = 22.65, SD = 3.10). Seventeen participants were female. Six participants identified as black/African American, 16 as white, 11 as Asian, 1 as native Hawaiian or other Pacific Islander, and 7 identified as Hispanic. Participants were excluded if they met the following criteria: (1) current enrollment in another research study that could influence participation in the present study, (2) use of pain-related medications that could not be stopped 7 days before testing (e.g., NSAIDs, antihistamines, antidepressants, anticonvulsants, migraine medications, and cough suppressants), (3) history of psychiatric, psychological, or neurologic disorder, as well as medical conditions associated with chronic pain, (4) current medical condition that could affect study participation, (5) positive pregnancy test result in females, (6) presence of metal within the body, and (7) inability to provide informed consent. The University of Florida Institutional Review Board approved the present study. All participants provided written informed consent.

Experimental materials

Thermal stimuli during fMRI scanning periods were delivered using an MR-compatible, Peltier element-based stimulator (TSA-2001; Medoc Thermal Sensory Analyzer, Ramat Yishai, Israel). Temperatures produced by this device range from 33°C to 51°C. Participants reported subjective pain ratings to these stimuli using an electronic VAS, anchored by ''No pain'' and ''Most intense pain sensation imaginable.''

Experimental procedures

Due to individual differences in pain perception, each participant completed QST during a screening visit before fMRI scanning, designed to establish stimulus intensities that were painful for each individual. Thermal pulses were delivered on the dorsal aspect of each foot, beginning at 43°C and increasing by 1°C until tolerance or 51°C was reached. Participants rated pain intensity on an electronic VAS after each pulse. Temperatures for pain stimuli used during fMRI scanning were determined for each individual based on the lowest temperature rated between 40 and 60 (''Suprathreshold pain temperature'').

MRI scanning included one 3D anatomical and three functional MRI scans. The experimental paradigm used for all three functional scans consisted of 16 thermal pulses delivered in a random order to one of the four sites on the dorsal aspects of both feet such that each site was stimulated equally. The same temperature was used throughout and the same random order was used for all three fMRI runs. Each pulse lasted 4 sec, with a 12-sec interstimulus interval (ISI). Participants rated pain intensity following each stimulus, during the ISI, using a computerized VAS (0–100), which was anchored by ''No pain sensation'' and ''Most intense pain sensation imaginable.''

Data acquisition and preprocessing

The MRI session took place on a 3.0T research-dedicated Philips Achieva scanner (8-channel head coil). High-resolution structural data were collected using a T1-weighted MP-RAGE protocol (180 1 mm sagittal slices, matrix [mm] = $240 \times 240 \times 180$, repetition time [TR] = 8.1 msec, echo time [TE] = 3.7 msec, FOV [mm] = $240 \times 240 \times 180$, FA = 8°, voxel size = 1 mm^3). Functional MRI used an echo planar acquisition protocol (38 contiguous 3 mm transaxial slices, matrix [mm] = $80 \times 80 \times 30$, TR/TE = 2000/30 msec, FOV [mm] = $240 \times 240 \times 114$, FA = 80°, voxel size = 3 mm^3). Each scan lasted 5 min and 40 sec, and all three runs used in the present analyses were conducted consecutively.

Image preprocessing was conducted using SPM12 (Wellcome Trust Centre for Neuroimaging, London, United Kingdom) with MATLAB 2011b (MathWorks, Sherbon, MA). Preprocessing of the fMRI data included slice-scan-time correction and volume registration/motion correction. The structural data were coregistered to the functional data before warping both sets into the common MNI stereotaxic space and spatially smoothing the fMRI data with an isotropic 6-mm Gaussian kernel (FWHM).

General linear model

To ensure that pain-related brain activation was elicited by the experimental protocol, a mass univariate general linear

model (GLM) was used to identify cortical regions in which pain stimuli onset was significantly convolved with the hemodynamic response function (HRF). The individual (first-level) analyses modeled the canonical HRF, and also temporal and dispersion derivatives. Artifact removal was performed with the Artifact Detection Tools (ART; www.nitrc.org/projects/artifact_detect) toolbox using the following parameters: global signal z-threshold = 3, absolute motion threshold = 0.5 mm, absolute rotation threshold = 0.01°, scan-to-scan motion threshold = 0.5 mm, and scan-to-scan rotation threshold = 0.01°. Volumes identified as outliers were entered into the design matrix as regressors of no interest. At the second level, a random effects GLM (RFX-GLM) was used to analyze individual contrast images using a one-sample *t*-test (pFWE ≤0.05), with a cluster size threshold of 5 voxels ($k \geq 5$).

Dynamic causal modeling

DCM (Friston et al., 2003) was used to estimate the interhemispheric effective connectivity among the rDLPFC and lDLPFC and perform model selection (DCM12; Wellcome Trust Centre for Neuroimaging, London, United Kingdom). DCM models changes in neural population interactions due to experimental and contextual manipulations, which are then inverted to generate a modeled BOLD signal. Modeled BOLD signals then compared to observed BOLD data to determine model fit. The application of DCM for fMRI allows for the comparison of hypothetical models of neural dynamics and statistical inference on connectivity parameter estimates. The present study used bilinear, deterministic DCM with mean-centered parameter estimates. These provide estimates of three classes of connectivity parameters: (1) experimental inputs estimate the effect of experimental conditions on regional activity; (2) endogenous connections, estimate of average inter- and intraregional effective connectivity (i.e., connectivity in the absence of stimuli); and (3) bilinear modulatory parameters estimate the effects of experimental conditions on inter-regional connectivity (i.e., the change in connectivity during painful stimuli). DCM parameters are estimated with a Bayesian scheme from the observed BOLD signals, using empirical priors for the hemodynamic parameters and conservative shrinkage parameters for the connectivity parameters (Friston et al., 2003). Previously, DCM has been successfully used to infer transcallosal connectivity and its modulation (David et al., 2011).

To identify the optimal model, the random effects Bayesian model selection (BMS) (Stephan et al., 2009) was used to compare hypothesized models of transcallosal DLPFC connectivity. BMS produces exceedance probabilities (EPs) for each model, to identify an optimal or winning model. EPs represent the certainty that a given model is more likely to explain the data compared to all others tested. Furthermore, EPs measure each DCM accuracy in modeling the observed data and are penalized by the complexity of the model, as such EPs reflect a balance of accuracy and complexity.

BMS proceeded in two steps. In Step 1, the best fitting model of only endogenous connectivity was identified from a set of models estimating unidirectional and bidirectional transcallosal influence (Fig. 1). Using the endogenous structure identified in Step 1, modulatory connections were then estimated to determine whether the painful stimuli altered interhemispheric connectivity (Step 2). In both cases, the winning model demonstrated the highest EP.

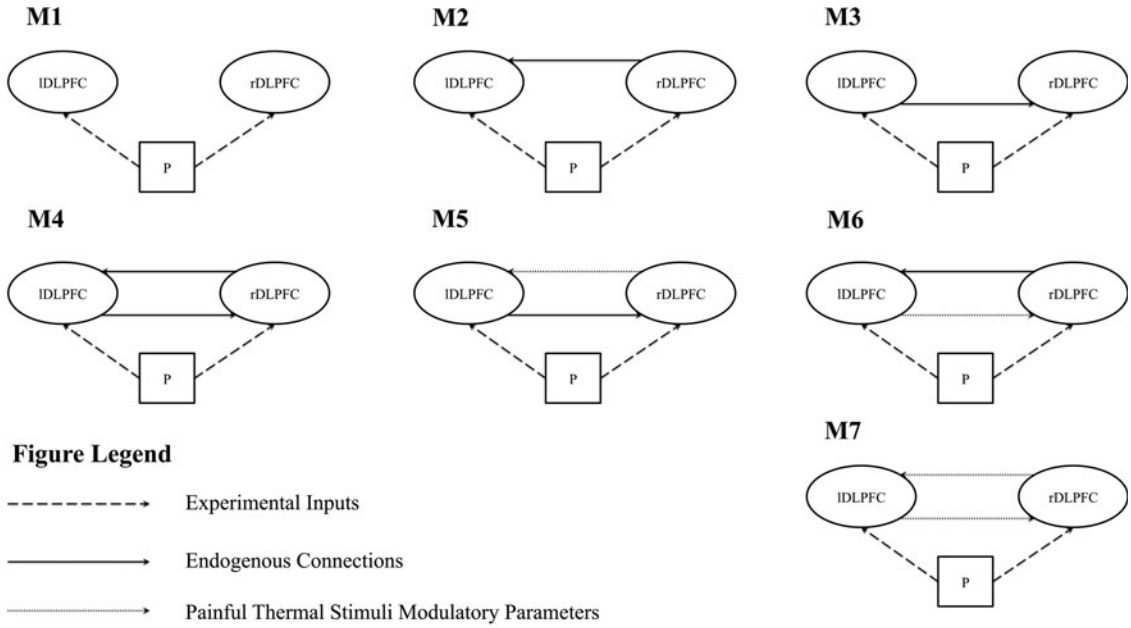

FIG. 1. Step 1 BMS compared the evidence for models containing only endogenous connections (M1–4). Step 2 BMS further compared evidence for models containing modulatory connections (M5–7), or effects of experimental inputs on interregional connectivity, against the winning model of Step 1 (M4). BMS, Bayesian model selection.

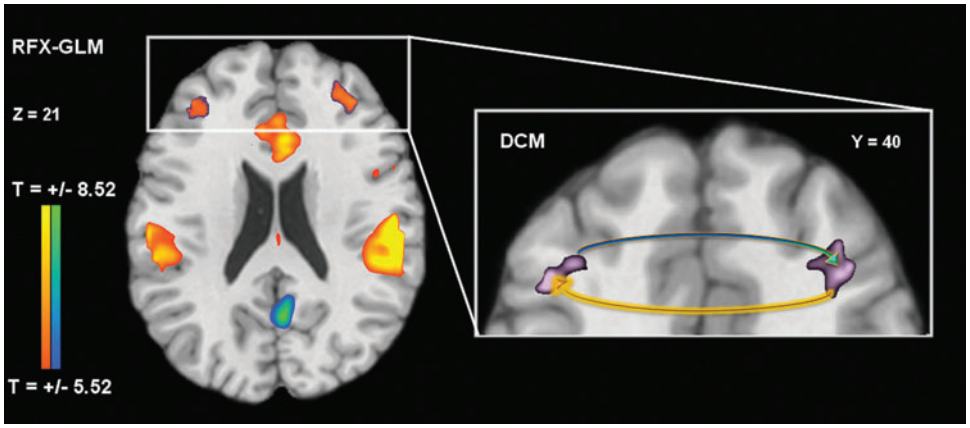

FIG. 2. Left: Significant activations (''pain'' vs. ''rest,'' pFWE ≤ 0.05, $k \geq 5$) were observed within regions of interest in both the right and left DLPFC (outlined in purple). Color bars indicate the range of suprathreshold T-scores within the GLM results. Right: BMA endogenous and modulatory interhemispheric connectivity parameters among the right and left DLPFC are displayed. Line and glow width are weighted on parameter estimate values (blue indicates negative estimates; yellow indicates positive). GLM, general linear model.

Regression analyses

To further clarify the role of interhemispheric DLPFC connectivity estimates and pain processing, a multiple linear regression was performed. Inter-regional endogenous connectivity parameters and bilinear modulatory parameters served as predictor variables with individual suprathreshold pain temperature as the criterion variable. Individual parameter values were determined to be significant at $p \leq 0.05$.

Time series extraction

Time series were extracted using both functional and anatomical constraints to avoid biasing regression results (Brodersen et al., 2011). The first eigenvariate was extracted from a 6 mm^3 sphere around the peak voxel ($p < 0.05$, uncorrected) within an anatomical mask of the DLPFC for each hemisphere. The DLPFC is often considered to consist of Brodmann areas (BA) 9/46, and sometimes 8/10 (Petrides, 2005). Anatomical masks consisted of the intersection of BA 8/9/10/46 and the middle frontal and superior frontal gyri (Brodersen et al., 2012). Anatomical masks were generated with the WFU PickAtlas (Maldjian et al., 2004, 2003). Subjects were excluded from DCM analyses if they failed to exhibit suprathreshold activation in response to thermal stimuli in both regions during all three runs.

Results

Group-level random effects GLM

During fMRI scanning, mean VAS pain ratings were 42.14 (SD = 14.53). Significant group-level activations within DLPFC masks were observed in both the left and right hemisphere (pain vs. rest): rDLPFC: $t(34) = 6.18$, pFWE = 0.01, $k = 5$; lDLPFC: $t(34) = 6.58$, pFWE = 0.003, $k = 5$. Figure 2 (left) depicts brain activity associated with suprathreshold pain stimuli in these regions.

Dynamic causal modeling

Five subjects did not display suprathreshold activation in one or both regions of interest. As a result, subsequent DCM analyses used only data from the remaining 30 subjects.

Bayesian model selection

Random effects BMS was first performed on a set of models in which only endogenous connections were specified (Table 1). Step 1 BMS indicated that a model, including bidirectional influence among the rDLPFC and lDLPFC, was the best balance of accuracy and complexity given the data (EP = 83.5%). This model was used as foundation to determine which transcallosal connections are modulated during exposure to suprathreshold painful stimuli in Step 2. Three additional models were specified and compared using BMS (Fig. 1). Step 2 BMS found evidence only for models including pain-related modulation of interhemispheric connectivity (M5–M7). However, among them there was no clear optimal model. In light of this variability between subjects, Bayesian model averaging (BMA) (Penny et al., 2010) was used to calculate average parameter estimates across models 5 through 7. BMA weighs the computation of parameter estimates upon the posterior probability across different models and is thus sensitive to random effects variability. The resulting average parameter estimates are shown in Tables 2 and 3. Endogenous and modulatory parameter estimates are depicted in Figure 2 (right). Results indicate that the rDLPFC → lDLPFC coupling functions to increase lDLPFC activity over time (mean endogenous parameter estimate = 0.12, SD = 0.00) and that this relationship is strengthened

TABLE 1. BAYESIAN MODEL SELECTION RESULTS

Step 1	M1	M2	M3	M4
	0.00	0.06	0.10	0.84
Step 2	M4	M5	M6	M7
	0.00	0.38	0.09	0.53

EPs for each model compared in both Step 1 and Step 2 Bayesian model selection are shown above. EPs are a quantitative representation of each model's balance of complexity and accuracy in predicting the observed BOLD data.

EPs, exceedance probabilities.

Table 2. BMA Endogenous and Modulatory Parameter Estimates

Parameter	*Endogenous mean (SD)*	*Modulatory mean (SD)*
rDLPFC → lDLPFC	0.12 (0.00)	0.50 (0.03)
lDLPFCC → rDLPFC	−0.64 (0.01)	0.19 (0.01)

Endogenous connections are estimates of average inter-regional effective connectivity. Bilinear modulatory parameters are estimates of the effects of experimental conditions on inter-regional connectivity.

BMA, Bayesian model averaging; rDLPFC, right dorsolateral prefrontal cortex; lDLPFC, left dorsolateral prefrontal cortex; SD, standard deviation.

during thermal stimuli (mean modulatory parameter estimate = 0.50, SD = 0.03). While the lDLPFC-rDLPFC coupling functions to decrease rDLPFC coupling over time (mean endogenous parameter estimate = −0.64, SD = 0.01), this relationship is weakened during thermal stimuli (mean modulatory parameter estimate = 0.19, SD = 0.01).

Regression analyses

BMA endogenous and modulatory parameter estimates were entered as predictor variables in a multiple linear regression with suprathreshold pain temperatures (mean = 48.79, SD = 1.55) as the criterion variable. Results showed that suprathreshold pain temperatures were significantly predicted by inter-regional endogenous and bilinear modulatory parameter estimates [$F(4, 25) = 2.74$, $p = 0.05$, $R^2 = 0.31$]. Parameter estimates (Table 4) indicate that the rDLPFC → lDLPFC endogenous and bilinear modulatory parameter estimates significantly predicted variance in suprathreshold pain temperatures ($\beta = 0.44$, $p = 0.018$, and $\beta = 0.41$, $p = 0.028$, respectively). In both cases, a significant positive association between parameter strength and emperature was observed.

Discussion

Numerous studies have indicated that the DLPFC plays a vital role in both pain processing and modulation. Much of this research, however, has focused on the modulatory action of the DLPFC in relation to ipsilateral regions. More recently, studies utilizing noninvasive brain stimulation have suggested that interhemispheric DLPFC connectivity may also be uniquely involved in pain processing (de Andrade et al., 2011; Graff-Guerrero et al., 2005). The present study sought to examine transcallosal DLPFC connectivity during the processing of painful stimuli and to determine whether this connectivity is associated with individual differences in suprathreshold pain sensitivity. DCM was used to estimate the connectivity between the lDLPFC and rDLPFC during painful thermal stimuli. Our results suggested that the reciprocal influences among these regions were enhanced during painful stimuli and that the greater rDLPFC → lDLPFC connectivity is associated with higher suprathreshold pain temperatures in our sample, indicating an inhibitory effect.

Table 3. BMA Experimental Input Parameter Estimates

Parameter	*Mean (SD)*
rDLPFC	0.21 (0.01)
lDLPFC	0.19 (0.01)

Experimental inputs are estimates of the effect of experimental conditions on regional activity.

Table 4. Regression Parameter Coefficients

Predictor	*Parameter class*	B	*SE*	*Beta*	t	p
rDLPFCC → lDLPFC	Endogenous	2.473	0.977	0.440	2.530	0.018
lDLPFCC → rDLPFC	Endogenous	0.963	0.889	0.181	1.083	0.289
rDLPFCC → lDLPFC	Modulatory	0.707	0.303	0.407	2.331	0.028
lDLPFCC → rDLPFC	Modulatory	0.269	0.281	0.163	0.957	0.348

Bayesian model selection

Random effects BMS was used to compare the relative balance of accuracy and complexity among estimated DCMs to identify those that best explained the data obtained in our ROIs. Step 1 BMS, which compared only endogenous connections, was most supportive of mutual endogenous influence of the lDLPFC and rDLPFC on each other (Model 4). In Step 2, this model acted as a null hypothesis (i.e., painful stimuli do not modulate effective connectivity among these regions), and modulatory parameters were added to test how painful stimuli influence DLPFCs mutual relationship in additional models (Models 5–7). Models 5–7 outperformed Model 4, suggesting that painful stimuli influence the connectivity of transcallosal DLPFC. However, as there was no single winning model, it is likely that exactly how painful stimuli influence this relationship varies at the individual level.

Examining the directionality of influences, BMA parameter estimates (Tables 2 and 3) showed that in the absence of painful stimuli (i.e., during the ISI), the rDLPFC functions to increase the lDLPFC activity (i.e., positive relationship), while the lDLPFC functions to decrease the rDLPFC activity (i.e., negative relationship). When modulatory parameters are added (i.e., change in connectivity during painful stimuli), directionality of influences changes. During thermal stimulation, both rDLPFC → lDLPFC and lDLPFC → rDLPFC couplings have positive relationships (modulatory parameter means = 0.50 and 0.19, respectively). However, when accounting for both BMA endogenous and modulatory parameters, the coefficient of the lDLPFC → rDLPFC relationship does not exceed 0, which suggests that there is a negative relationship between these regions that weakens as a result of painful stimuli. Taken together, painful stimulation results in an increase in the positive influence of the rDLPFC on the lDLPFC, and a decrease in negative feedback from the lDLPFC to rDLPFC. This may be indicative of increased rDLPFC influence during painful stimuli.

Regression analyses

Individual suprathreshold pain temperatures were regressed on endogenous and modulatory effective connectivity parameter estimates to further examine the role of interhemispheric

DLPFC connectivity. Results indicated that parameter estimates explained a significant proportion of variance in suprathreshold pain temperatures ($R^2 = 0.31$). Specifically, greater values of both the rDLPFC → lDLPFC endogenous and modulatory parameters were found to be significantly associated with higher individual pain temperatures. In light of this, our results suggest that individuals with greater endogenous influence from the rDLPFC to the lDLPFC require a greater temperature to experience a similar amount of pain. Likewise, those who experience greater modulatory enhancement of rDLPFC → lDLPFC connectivity in the context of painful stimuli also tend to require a higher temperature to experience similar amounts of pain, potentially suggesting a greater pain modulatory capacity.

Consistent with previous research, our findings provide further support for the influential role of the right hemisphere in pain processing (Coghill et al., 2001; Symonds et al., 2006), and for the role of interhemispheric connectivity in maintaining functional hemispheric asymmetries (Kaller et al., 2015). Furthermore, the DLPFC has been implicated in the processes of monitoring and manipulating information, and working memory in the context of pain processing (Craggs et al., 2007). Likewise, tDCS of the DLPFC, with potentially excitatory effects on the rDLPFC and inhibitory effects on the lDLPFC, was found to increase thermal pain thresholds and improve performance on a working memory task (Mylius et al., 2012). These authors argued that interhemispheric inhibition of the left hemisphere might have played a role in these changes. It is possible that evaluative, monitoring, and working memory processes are involved in our findings as well.

Implications and limitations

Although multiple investigations of the effects of noninvasive brain stimulation in pain have implicated alterations of interhemispheric connectivity in increased pain tolerance, our study is the first to demonstrate that transcallosal DLPFC connectivity may play an important role in pain perception in the absence of noninvasive brain stimulation such as rTMS or tDCS. Our findings may similarly be important for guiding future investigations and provide a potential mechanism and assessment target to determine the long-term effects of noninvasive brain stimulation on neural functioning. As our results only concern healthy individuals, and increased pain sensitivity is commonly associated with chronic pain conditions, investigation of the role of DLPFC interhemispheric connectivity in patient populations may also provide valuable information about the mechanisms behind increased pain sensitivity in chronic pain. Given the connectivity structures elucidated in the present study, future investigations examining the implications of these structures on couplings with other regions (e.g., between the DLPFC, ACC, SI/SII) are needed to contextualize our results within the distributed set of regions involved in pain processing.

Interhemispheric projections have been implicated in both excitatory and inhibitory processes; a recent review suggests that these connections likely serve both functions in a context- and task-specific manner (Bloom and Hynd, 2005). Therefore, studies capable of examining neural functioning at a more detailed level than fMRI or perhaps comparative studies are necessary to further clarify the nature of these relationships as they relate to our findings.

The results of the present study are correlational in nature and experimental designs will be necessary to validate a causal relationship between interhemispheric connectivity and thermal stimulus sensitivity. Previous studies, which presumably altered connectivity with rTMS or tDCS, suggest that interhemispheric connectivity plays a role in pain tolerance. However, it is also possible that our results are indicative of the influence of higher stimulus temperatures on interhemispheric connectivity as no direct manipulation was used in our study. It should also be noted that in fMRI connectivity methods, causality inferred by temporal lag, such as those imposed in DCM, represents a combination of neural lag and hemodynamic delays, potentially preventing certain causal inferences (Smith, 2012).

Conclusion

The role of the DLPFC in pain modulation through pathways to ipsilateral structures (e.g., PAG) is well established. Although recent brain stimulation studies have implicated interhemispheric DLPFC inhibition as a mechanism underlying changes in pain tolerance, to our knowledge, no other studies have examined the role of interhemispheric DLPFC effective connectivity in pain processing. The results of the present study indicate that not only is the interhemispheric connectivity among the rDLPFC and lDLPFC dynamically modulated during thermal stimuli, but also that individual differences in rDLPFC → lDLPFC couplings are associated with individual differences in the temperature needed to elicit suprathreshold pain. This relationship may be used as a mechanism to better understand endogenous pain modulation, including the mechanisms underlying hyperalgesia in chronic pain populations.

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Author Disclosure Statement

No competing financial interests exist.

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