



Predicting trait-like individual differences in fear of pain in the healthy state using gray matter volume

Xiaowan Wang¹ · Chris Baeken^{2,3,4} · Mengxia Fang⁵ · Jiang Qiu¹ · Hong Chen¹ · Guo-Rong Wu¹ 

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Abstract

Fear of pain (FOP) can be considered as a product of evolution from overstated negative interpretations of pain and sometimes may cause more damage than the actual pain itself. While trait-like measures of FOP have emerged as predictors for the inception and development of chronic pain, its neural underpinnings are not well understood. To investigate the relationship between gray matter volumes (GMV) and trait-like individual differences in FOP, we analyzed structural magnetic resonance imaging data in a sample of healthy young adults. Regression analysis results showed that individuals with higher FOP scores displayed higher GMV in brain regions important for the regulation of pain and fear. These brain areas include the pregenual anterior cingulate cortex (ACC), the anterior part of the dorsal ACC, the dorsomedial prefrontal cortex, and the adjacent pre-supplementary motor area. Furthermore, cross-validation analysis confirmed that the identified regional GMV offered a reliable neural signature of trait-like FOP. Our findings shed more light on the neuroanatomical architecture of FOP in currently pain-free people, which may be helpful to guide early interventions to prevent FOP from becoming chronic.

Keywords Fear of pain · Gray matter volume · Anterior cingulate cortex · Dorsomedial prefrontal cortex · Cross-validation

Introduction

Unpleasant experiences of pain potentially induce exaggerated negative cognitive distortions, which may eventually evolve into fear of pain (FOP) (Simons 2016; Turk and Wilson 2010). FOP can affect many aspects of daily life, such

as the occurrence of avoidance behaviors (Suhr and Spickard 2012; Swinkels-Meewisse et al. 2006; Thomas and France 2007; Vlaeyen and Linton 2000) and the misperception of pain intensity (Hirsh et al. 2008; Kirwilliam and Derbyshire 2008). Importantly, trait-like measures of FOP have been regarded as powerful predictors of the development of pain-related disabilities (Black et al. 2015; Crombez et al. 1999; Trost et al. 2011). The updated fear-avoidance (FA) model indicates that a vicious circle of FOP and associated avoidance behaviors, also in currently pain-free individuals, increases the risk of developing chronic pain (Crombez et al. 2012; de Jong et al. 2012; Leeuw et al. 2007; Vlaeyen and Linton 2012; Zale and Ditre 2015).

Functional neuroimaging studies focusing on FOP have yielded inconsistent results to date (Barke et al. 2012; Barke et al. 2016; Leeuw et al. 2007; Salomons and Davis 2012). In line with the FA model, several studies have found that higher FOP level is associated with stronger activation in fear-related brain regions induced by the observation of harmful movements (Barke et al. 2016; Michael Lukas Meier et al. 2017; Michael L Meier et al. 2015; Michael L Meier et al. 2016). There are also studies that have failed to confirm the hypothesis of the FA model (Barke et al. 2012; Taylor et al. 2015). In addition to the small sample sizes, another explanation for the

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✉ Guo-Rong Wu
gronwu@gmail.com

¹ Key Laboratory of Cognition and Personality, Faculty of Psychology, Southwest University, Chongqing, China

² Department of Psychiatry and Medical Psychology, Ghent University, Ghent, Belgium

³ Department of Psychiatry, Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZBrussel), Laarbeeklaan 101, 1090 Brussels, Belgium

⁴ Ghent Experimental Psychiatry (GHEP) Lab, Ghent University, Ghent, Belgium

⁵ Department of Art Education, Chongqing Vocational College of Applied Technology, Chongqing, China

discrepancies could be that passively viewing pictures of aversive movements may not be enough to evoke fear of actually experiencing pain (Barke et al. 2016; Salomons and Davis 2012). Most of the aforementioned neuroimaging studies have been carried out in chronic pain patients, but little is known about the neural influence of FOP in pain-free individuals. A better understanding of the neuroanatomical substrates underlying trait-like FOP in pain-free people may be necessary to better comprehend our insights into the possible mechanisms underlying pain-related disabilities.

Voxel-based morphometry (VBM) is an objective approach to examine the neural bases of trait-like characteristics (e.g. FOP) without task performance confounds, and this technique has been proven very useful in characterizing subtle anatomical changes related to chronic pain (Kumbhare et al. 2017; Mechelli et al. 2005; Smallwood et al. 2013; Whitwell 2009). In the current study, we aimed to examine the structural neural correlates of trait-like FOP by applying the VBM method in a large sample of healthy young adults, and hypothesized that trait-like FOP scores would be associated with gray matter volumes (GMV) in brain regions engaged in pain and fear, the two core aspects of FOP.

Materials and methods

Participants and procedures

A total of 99 young healthy subjects (58 females; mean age = 19.81, SD = 1.06, 17–25 years) from Southwest University were included in the current study. All participants were right-handed and none of them reported a history of major medical (e.g. chronic pain) or neuropsychiatric illnesses or substance abuse. Each participant was assessed with a structural magnetic resonance imaging (MRI) scan and a fear of pain questionnaire.

Fear of pain measurement

The Fear of Pain-5 (FOP-5) questionnaire, a 5-item scale included in the Pain Anxiety Symptoms Scale, was used to assess fear in relation to pain (McCracken and Dhingra 2002). All items are rated on a 6-point frequency scale ranging from 0 (never) to 5 (always). The total score is computed by summing all five items (maximum score is 25). Compared to their lower-scoring counterparts, people with higher FOP scores are more likely to have fearful thoughts about pain and are more prone to anticipate negative consequences of pain (Abrams et al. 2007; McCracken and Dhingra 2002). The FOP-5 has good internal consistency in this study ($\alpha = 0.67$), supporting the validity of the derived scores as indices of trait-like FOP.

MRI acquisition

Magnetic resonance images were obtained using a 3 T Siemens Tim Trio MRI scanner (Siemens Medical Solutions, Erlangen, Germany) with a 12-channel head coil in the Brain Imaging Center of Southwest University. High-resolution 3D T1-weighted anatomical scans were collected using a magnetization-prepared rapid gradient echo (MPRAGE) sequence (176 sagittal slices; repetition time = 1900 ms; echo time = 2.52 ms; inversion time = 900 ms; flip angle = 9°; voxel size = $1 \times 1 \times 1 \text{ mm}^3$; slice thickness = 1.0 mm).

Voxel-based morphometry

VBM analysis was performed using the SPM12 (<http://www.fil.ion.ucl.ac.uk/spm>). First, each T1 weighted anatomical image was manually reoriented, setting the origin in the anterior commissure. Then, the anatomical images were segmented into gray matter (GM), white matter and cerebrospinal fluid. Subsequently, a sample-specific template (across all subjects) was created using DARTEL toolbox in SPM12 (Ashburner 2007). The segmented GM images were spatially normalized into the sample-specific template and affine-aligned into a Montreal Neurological Institute (MNI) space. Finally, the spatially normalized GM images were modulated by Jacobian determinants and smoothed with a 10-mm full-width at half-maximum Gaussian kernel.

Statistical analysis

We firstly performed a whole-brain voxel-wise multiple regression analysis to identify regions of GMV associated with trait-like FOP levels. Age, gender, and total intracranial volume (TIV) were included as nuisance covariates. The statistical inferences were performed at $p < 0.05$, cluster-level family-wise error (FWE) corrected for multiple comparisons using the Gaussian random field theory, with uncorrected voxel-level $p < 0.001$. We then conducted a confirmatory analysis using a 3-fold cross-validation procedure combined with L2-regularized model to investigate the robustness of VBM findings (Evans et al. 2015; Abrams et al. 2016). The GMV-based profiles were entered as independent variable and the FOP score as dependent variable. To eliminate bias caused by random division, data were divided into three different folds according to FOP scores so that the score distributions across folds were balanced (Cui et al. 2017). A L2-regularized model was built with two-fold data and then applied to predict the data in the remaining fold (Pedregosa et al. 2011). The Pearson correlation r , as well as the mean squared error (MSE) were computed between the observed and estimated FOP scores. Finally, a permutation test was carried out to

Table 1 Demographic information ($n = 99$)

	All	Males	Females	<i>P</i> value
# subjects	99	41	58	0.088
Age	19.81(1.06)	19.95(1.14)	19.71(0.99)	0.259
FOP-5	6.23(3.46)	6.20(3.56)	6.26(3.43)	0.929

Means were reported with their standard deviation (SD) in parentheses. *P*-values: males versus females

assess the statistical significance of the prediction (randomly shuffle FOP scores 1000 times).

Results

Fear of pain scores

Table 1 shows the descriptive statistics on the demographic characteristics and FOP scores (mean±SD: 6.23±3.46, range: 0–16). No significant gender difference in FOP scores was found [$t(97) = -0.089$, $p = 0.929$].

GMV-based features predicting FOP scores

As presented in Table 2 and Fig. 1, there were significantly positive associations between FOP scores and GMV in several brain regions, including the dorsomedial prefrontal cortex (dmPFC), the pre-supplementary motor area (pre-SMA), the anterior part of the dorsal anterior cingulate cortex (adACC), and the pregenual anterior cingulate cortex (pgACC) ($p < 0.05$, cluster-level FWE corrected with uncorrected voxel-level $p < 0.001$, cluster size = 1639 voxels).

The associations between the identified regions and trait-like FOP were supported by the cross-validation test. As shown in Fig. 2, the estimated FOP scores had positive correlation with the observed scores (average $r = 0.41$, permutation test, $p < 0.001$; average MSE = 10.08, permutation test, $p < 0.001$). The estimated FOP scores for all three folds remained significantly correlated with the observed scores (average $r = 0.39$, permutation test, $p < 0.001$; average MSE = 10.51, permutation test, $p < 0.001$), using the 6-mm sphere centered on the peak MNI coordinate of the multiple regression analysis results (See Supplemental Fig. 1). In addition, it has been

proposed that demographics including age and gender account for a small portion of the variance of perceived pain associated with negative emotions (Baliki et al. 2006; Peters et al. 2005). Nonetheless, we found that these two non-specific variables could not significantly predict trait-like FOP levels in currently pain-free people.

Discussion

Although the role of fear in pain-related disability has been well established, little is known about the neural correlates of individual differences in fear in relation to pain. To address the above issue, we measured trait-like FOP and identified regional variations in GMV in healthy participants. In concordance with our hypothesis, participants with higher FOP scores displayed significantly higher GMV in brain areas involved in pain and fear processing, including the adACC, pgACC, dmPFC, and the adjacent pre-SMA.

The adACC constitutes a critical hub implementing a domain-general function across negative affect (e.g. fear), pain, and cognitive control (Price 2000; Shackman et al. 2011; Shenhav et al. 2013; Stevens et al. 2011; Vogt 2005). Specifically, this region has been thought to mediate the fear-avoidance aspect of pain processing (Vogt 2005). A recent framework termed *The Adaptive Control Hypothesis (TACH)* postulates that adACC uses information about negative reinforcers to adopt the most adaptive aversively-motivated behaviors (Cavanagh and Shackman 2015; Shackman et al. 2011). The ‘expected value of control (EVC) model’ also proposes that the dorsal anterior cingulate cortex (ACC) is responsible for adaptively adjusting the allocation of cognitive control and action selection (Shenhav et al. 2013). Since individuals with higher trait-like FOP levels more frequently scan the environment for potential sources of pain and are more eager to detect ‘threatening’ stimuli, one could assume that such individuals exhibit adaptive fear-avoidance actions (Van Damme et al. 2002; Van Damme et al. 2004). Taken together, our findings indicate that pain-related fear has a neural impact on pain-free individuals, and such effect may be associated with increased avoidance behaviors. This fits well with the key hypothesis of the FA model that fear of pain motivates avoidance behaviors and consequently contributes to the risk of chronicity.

Table 2 Brain regions with significant associations between GMV and trait-like FOP scores

Brain regions	Brodmann area	Cluster size (# voxels)	Peak <i>T</i> -value	Peak MNI coordinates		
				x	y	z
dmPFC	6/8/9/10	771	4.90	−8	49	23
Pre-SMA	6	268	3.99	0	15	51
ACC	9/10/32	556	3.58	14	33	20

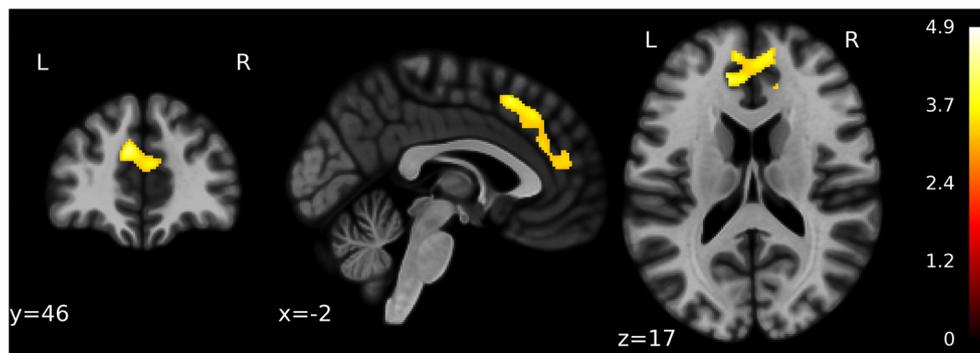


Fig. 1 Regression analysis between GMV and trait-like FOP scores. The significantly larger GMVs in people with higher FOP scores are shown in hot colors: adACC, pgACC, dmPFC, pre-SMA. The results are shown

with $p < 0.05$, FWE corrected for multiple comparisons at the cluster level with an underlying uncorrected voxel level of $p < 0.001$. Age, gender, and TIV were included as nuisance covariates

The dmPFC is a common region involved in the processing of both pain and fear (Etkin et al. 2011; Lamm et al. 2011), and further substantially contributes to the production of aversive memories for painful experiences (Euston et al. 2012). Even in the absence of any external stimuli the dmPFC is still prominently activated by negative emotions (e.g. fear) (Ashar et al. 2017; Lindquist et al. 2012). As part of the social mentalizing network (Amodio and Frith 2006; Blakemore 2008; Van Overwalle 2009), the dmPFC is consistently recruited in inferring the intensity of others' affective experience of pain (Jackson et al. 2006; Lamm et al. 2007; Morelli et al. 2015). Similarly, the dorsal anterior cingulate cortex and the pre-SMA are involved in empathic processes when others are experiencing pain (Lamm et al. 2011).

The pgACC is consistently tied to the processing of the affective component of pain (e.g. fear) (Shackman et al. 2011; Vogt 2005). Etkin et al. (2011) highlighted that the pgACC played a critical role in top-down emotion regulation strategies, such as emotional conflict regulation. Meta-analytic research also indicated consistent engagement of the dmPFC, the dorsal ACC, and the pre-SMA in implementing executive control over emotional processing (Buhle et al. 2014; Etkin et al. 2015; Kalisch 2009; Kohn et al. 2014).

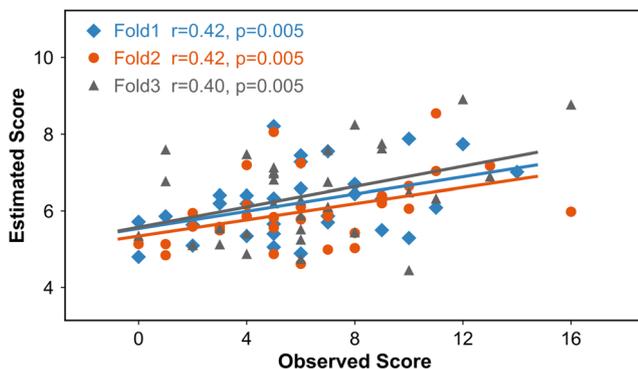


Fig. 2 Cross-validated prediction of FOP scores. The estimated FOP scores had significantly positive correlation with observed scores in each of the three folds. First fold, $r = 0.42$, $p = 0.005$; second fold, $r = 0.42$, $p = 0.005$; third fold, $r = 0.40$, $p = 0.005$. All the p values above were calculated using permutation tests (1000 times)

The increased GMV in these regions may point to the neural substrates implicated in the multiple emotional regulation strategies of pain-related fear responses in healthy young individuals. According to recent research on neuroplasticity and pain chronification, the observed higher regional GMV in people with higher FOP scores could be the consequence of the more frequent involvement in pain-related fear responses (Neeb et al. 2017). In addition, our results are in line with previous findings that the increases in regional GMV may primarily occur in younger individuals with short pain duration (Ceko et al. 2013; Kumbhare et al. 2017; May 2011; Younger et al. 2010).

Pain treatment designed to target FOP processes has become an attractive therapeutic option to reduce pain-related disability by extinguishing maladaptive fear-learning patterns (Leeuw et al. 2007; Leeuw et al. 2008; Simons et al. 2015; Zale et al. 2013). Our observed neuroanatomical brain areas for FOP in pain-free individuals could be harnessed for novel brain-based FOP assessments (Gabrieli et al. 2015), contributing to the development of earlier and more effective treatment interventions.

Several limitations warrant comments. Firstly, the interpretations of our findings are limited to young adults (age range: 17–25 years). Although a cross-validation procedure was used to ensure the robustness of GMV-FOP relationships, the training and testing data were not completely independent. Future studies are necessary to include different data sets to test the generalization of our findings. Secondly, in addition to sociodemographic characteristics (age and gender), other nuisance variables (e.g. pain catastrophizing) accounting for GMV differences should be controlled to make the results more reliable in future studies. Lastly, the morphology and function of white matter associated with FOP need to be further explored (Gawryluk et al. 2014; Ji et al. 2017).

In conclusion, the present study has identified regional GMV associated with the trait-like individual differences in FOP for healthy subjects. Specifically, participants with higher trait-like FOP scores displayed higher GMV in brain regions involved in pain and fear regulation. Our findings

provide neuroanatomical evidence for the possible impact of pain-related fear in currently pain-free people, and may be useful in adopting early interventions to prevent the development of enduring pain. Future studies may do well to incorporate multimodal brain imaging data, providing a more comprehensive understanding of the neural mechanisms of FOP.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This study was approved by the Institutional Human Participants Review Board of Southwest University Imaging Center for Brain Research and all participants gave written informed consent prior to their participation.

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