



The impact of pain-related fear on neural pathways of pain modulation in chronic low back pain

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Abstract

Introduction: Pain-related fear plays a substantial role in chronic low back pain (LBP) by amplifying the experienced disability. Related dysfunctional emotions and cognitions may also affect sensory aspects of pain through a modulatory pathway in which the periaqueductal gray (PAG) and the amygdala play key roles.

Objectives: We therefore hypothesized a differential amygdala-PAG functional connectivity (FC) in patients with chronic LBP that is modulated by the degree of pain-related fear.

Methods: We used data of a previously reported fMRI study where 20 chronic LBP patients (7 females, mean age = 39.35) and 20 healthy controls (12 females, mean age = 32.10) were asked to observe video clips showing potentially harmful and neutral activities for the back. Pain-related fear was assessed using the Tampa Scale of kinesiophobia (TSK) and Fear Avoidance Beliefs questionnaires (FABQ). Generalized psychophysiological interactions were used to reveal task-based FC.

Results: Compared to controls, patients exhibited a significant decrease in amygdala-PAG-FC ($P = 0.022$) during observation of harmful activities, but not of neutral activities. Furthermore, amygdala-PAG-FC correlated negatively with Tampa Scale of kinesiophobia scores in patients ($R^2 = 0.28$, $P = 0.01$) but not with Fear Avoidance Beliefs questionnaires scores.

Discussion: Our findings might indicate a maladaptive psychobiological interaction in chronic LBP patients characterized by a disrupted amygdala-PAG-FC that is modulated by the degree of pain-related fear. These results shed new light on brain mechanisms underlying psychological factors that may have pronociceptive effects in chronic LBP.

Keywords: Amygdala, PAG, Chronic low back pain, fMRI, PPI, Fear avoidance beliefs, Functional connectivity, Kinesiophobia

1. Introduction

Chronic low back pain (LBP) accounts for a considerable burden in terms of pain and suffering.^{2,19,21} Impaired endogenous pain modulation is likely one of the mechanisms contributing to the development and maintenance of chronic

pain.^{11,17,25} The neural circuit underlying emotion and pain modulation comprises 2 key structures that are highly related by sharing functional and structural connections, namely the amygdala and the periaqueductal gray (PAG).^{22,27,33} The amygdala constitutes an important site for a reciprocal relationship between persistent pain and negative affective states such as fear and anxiety.^{4,10,23,24,31} The PAG is a key region involved in pain modulation and thought to play an important role in the pathogenesis of chronic pain.^{5,14,33} In support, it has been shown that the resting-state functional connectivity (FC) of the PAG is disrupted in chronic LBP.³³ However, evidence about modulating factors of amygdala-PAG-FC in chronic LBP is sparse. One potential factor might be pain-related fear. Pain-related fear partly predicts LBP chronification, probably via a vicious circle of cognitive dysfunctions that may ultimately lead to physical deconditioning of the musculoskeletal system.^{1,12,29,32} Based on the knowledge that cognitions modulate not only emotional functioning but also sensory aspects of pain perception through endogenous pain modulatory mechanisms,²⁰ we hypothesized that pain-related fear modulates the neural crosstalk between the amygdala and the PAG. Therefore, we used an existing data set to specifically test amygdala-PAG-FC and its relationship with the individual degree of pain-related fear in chronic LBP patients and asymptomatic controls.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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2. Methods

2.1. Subject recruitment and questionnaires

The study was approved by the Ethics Committee Zurich (Switzerland) and conducted in accordance with the Declaration of Helsinki. Subjects provided written informed consent. The current study involved 20 patients suffering from nonspecific chronic LBP and 20 healthy gender-matched and age-matched controls (HC, **Table 1**). Pain-related fear was assessed with 2 questionnaires focusing either on fear of movement/(re)injury/kinesiophobia (Tampa Scale of Kinesiophobia questionnaire, TSK) or fear avoidance beliefs (Fear Avoidance Beliefs questionnaire, FABQ³⁰). Due to abbreviated, validated versions of the original 17-item TSK questionnaire, we additionally calculated the questionnaire scores of the 13-item and 11-item TSK versions.^{6,26} For detailed information about questionnaires, please see supplemental material (Available at <http://links.lww.com/PR9/A5>).

2.2. Imaging and experimental protocol

For image preprocessing and detailed description of the experimental protocol, please see supplemental material (Available at <http://links.lww.com/PR9/A5>). Briefly, participants viewed video clips (4 seconds) of activities potentially harmful for the back and control neutral activities in randomized order during fMRI. The activities were adapted from the electronic version of the Photograph Series of Daily Activities that has established a fear hierarchy based on patients' perceived harmfulness.^{13,16} In addition, our patients rated the clips during fMRI using a visual analog scale, confirming that potentially harmful activities were perceived as being more harmful compared to neutral activities (supplemental material, Available at <http://links.lww.com/PR9/A5>).

2.3. Amygdala-PAG-FC analysis

Using the same data set, we previously examined the FC of the amygdala with a whole brain analysis approach and observed that amygdala FC to the anterior insula differed between chronic LBP and controls as a function of the TSK score.¹⁶ Here, we subject the data to a secondary region of interest analysis based on the extensive a priori evidence regarding the involvement of the amygdala and PAG in emotion and pain regulation^{4,5,10,14,22}. To assess the temporal covariance between the amygdala and the PAG on the neural level, generalized psychophysiological interactions were computed.¹⁵ We

extracted the deconvolved time course across the bilateral amygdala defined on the Harvard-Oxford Cortical and Subcortical Structural Atlas (<http://www.fmrib.ox.ac.uk/fsl>) with a probability threshold of 50% (**Fig. 1A**). The psychological terms (harmful and neutral video clips), the physiological regressors (time courses of seed region) as well as the interaction terms and the movement parameters were included in the final model. Thus, the variance explained by the interaction term is only that over and above what is explained by the main effects of task and physiological correlation.¹⁸ Finally, the amygdala connectivity estimates (contrasts harmful activities > baseline and neutral activities > baseline) were computed for each subject using *rfxplot* (<http://rfxplot.sourceforge.net/>) with a study-independent mask of the PAG. The PAG mask consisted of bilateral 6-mm spheres each centered around the average peak location reported in a review of multimodal PAG responses including pain (left MNI xyz: -4, -29, -12/right MNI xyz: 4, -29, -12).¹⁴ The resulting connectivity estimates were analyzed in SPSS (version 23) with a repeated measures ANOVA (within-subject factor "condition" [harmful and neutral] and between-subject factor "group" [patients and controls]), followed by post hoc 2-sample *t* tests. Condition-specific relationships between questionnaire scores and FC were tested using Pearson's correlation coefficient and statistically compared using "cocor" (<http://comparingcorrelations.org/>) based on a modification of Fisher's *Z* procedure.^{3,8} Normality of the questionnaire data was assessed by using skewness and kurtosis indices of ± 2 .⁷

3. Results

3.1. Questionnaire scores

For questionnaire scores **Table 1**. Several significant correlations between the different pain-related fear questionnaires scores were observed (**Table 2**).

3.2. Amygdala-PAG-FC

There was no significant main effects of "group" or "condition" (P 's > 0.14), whereas the "group \times condition" interaction showed a trend ($F_{1,38} = 3.41$, $P = 0.072$). Post hoc *t* tests indicated a significant decrease in amygdala-PAG-FC in patients compared to controls during observation of the harmful activities (patients $M = 0.14$, $SD = 0.38$; HC $M = 0.44$, $SD = 0.40$, $t(38) = -2.385$, $P = 0.022$ [2-tailed]) but not during neutral activities (patients $M = 0.27$, $SD = 0.67$, HC $M = 0.22$, $SD = 0.43$, $t(38) = 0.296$, $P = 0.769$ [**Fig. 1B**]). Furthermore, during observation of harmful activities, the strength of the amygdala-PAG-FC in patients showed significant negative correlations with the TSK scales with the 13-item version demonstrating the strongest relationship ($R^2 = 0.28$, $P = 0.01$, **Fig. 1C**). The FABQ questionnaire and its subscales did not correlate with the amygdala-PAG-FC strength (P 's > 0.45). No significant relationships between amygdala-PAG-FC strength and questionnaire scores were observed during observation of neutral activities (P 's > 0.28). Direct comparison of the different TSK and FABQ correlation coefficients between the harmful and neutral conditions revealed no significant differences (P 's > 0.14).

4. Discussion

Our results might indicate a maladaptive psychobiological interaction in chronic LBP characterized by an attenuation of

Table 1
Participants' characteristics and questionnaire scores.

	Minimum	Maximum	Mean \pm SD
Healthy controls (N = 20)			
Age	19	69	32.10 \pm 10.78
Chronic low back pain (LBP) patients (N = 20)			
Age	21	62	39.35 \pm 13.97
Fear Avoidance Beliefs questionnaire (FABQ)-total	3	83	35.45 \pm 22.53
FABQ-activities	2	21	12.80 \pm 5.59
FABQ-work	0	40	15.50 \pm 12.12
Tampa Scale of kinesiophobia (TSK)-17	26	52	36.90 \pm 5.59
TSK-13	16	43	27.60 \pm 5.96
TSK-11	13	38	23.20 \pm 5.71

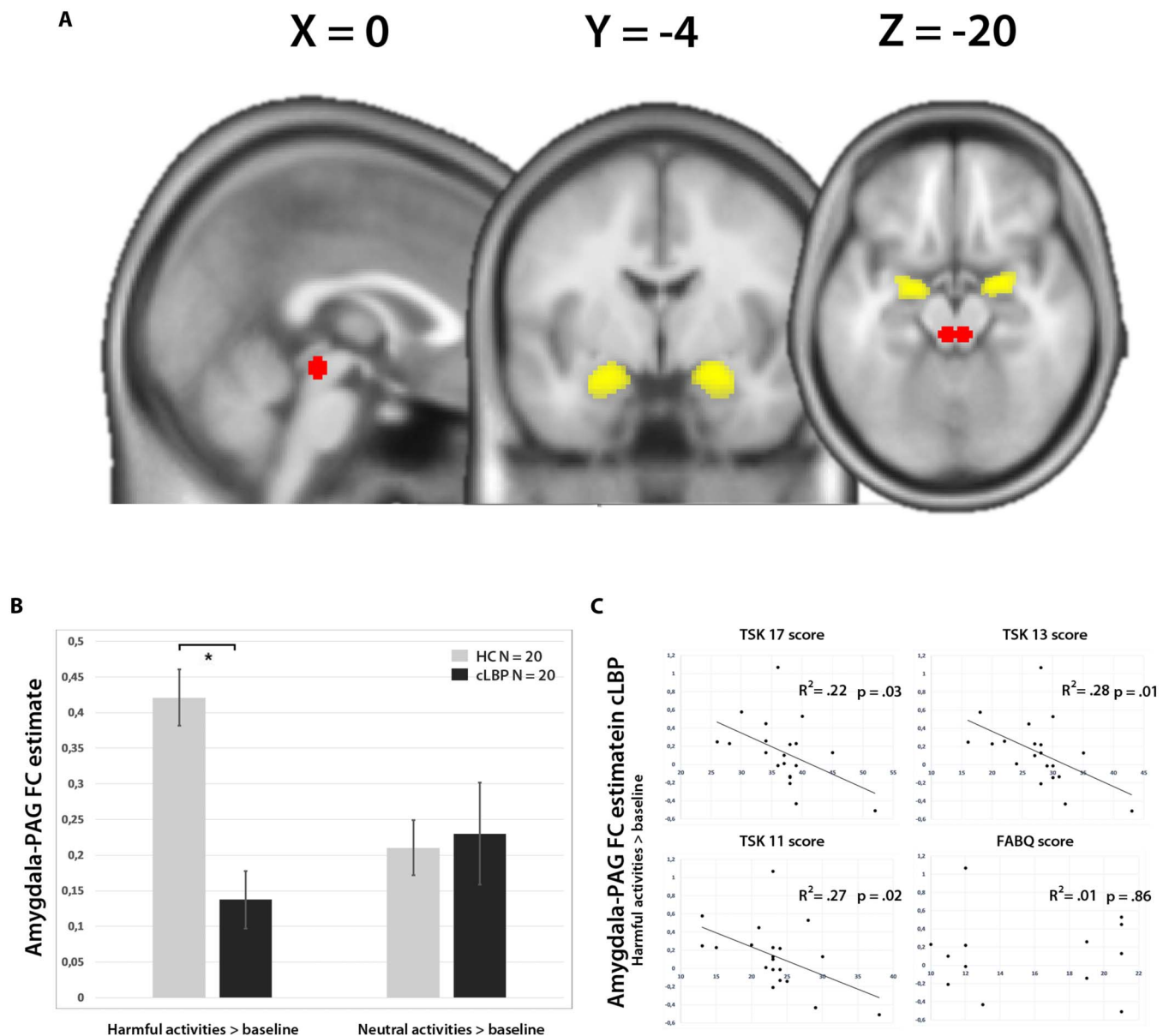


Figure 1. (A) Yellow color indicates the bilateral amygdala seed region (Harvard-Oxford Cortical and Subcortical Structural Atlas, $P > 0.5$). Red color indicates the bilateral 6-mm spheres around the PAG coordinates reported in Linnmann et al (2012). (B) Amygdala-PAG-FC strength between groups (chronic LBP vs HC) and conditions (harmful activities >baseline, neutral activities >baseline). (C) Correlations between amygdala-PAG-FC in chronic LBP patients and different pain-related fear questionnaires. T-bars represent standard error of the mean. PAG, periaqueductal gray; LBP, low back pain; HC, healthy controls.

amygdala-PAG-FC that is modulated by the degree of pain-related fear. Besides the established role of the PAG in the modulation of nociceptive inputs, our results add further evidence to the involvement of the PAG in negative emotional processing not directly related to nociception.^{9,28} Furthermore, while we have previously shown that pain-related fear is positively correlated with amygdala activity in chronic LBP,¹⁶ enhanced pain-related fear seems to simultaneously dampen the neural crosstalk between the amygdala and the PAG. This decreased information exchange between 2 key pain modulatory structures might ultimately tip the balance of PAG function to facilitation, ie, increased pronociception.¹¹ Thus, the decreased crosstalk between the amygdala and the PAG, in conjunction with increased amygdala activity, might be the neurobiological basis of how pain-related fear contributes to pain and its chronification. However, indicated by the nonsignificant interaction/correlations

(see results section 3.2), it must be noted that the potentially harmful video clips might elicit other reactions than fear such as processes associated with threat and defensive responses, which might impact the specificity of the findings. Interestingly, the TSK and the FABQ seem to capture different concepts of pain-related fear reflected in the differential brain-behavior relationships. More research is needed to increase the construct validity of these commonly used questionnaires including a new elaborate framework for pain-related fear to further enhance the specificity of its neural correlates.

Disclosures

The authors have no conflicts of interest to declare.

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Table 2
Correlations between pain-related fear questionnaires.

	Correlations					
	TSK-17	TSK-13	TSK-11	FABQ-total	FABQ-activities	FABQ-work
TSK-17						
Pearson Correlation	1	0.945*	0.959*	0.460†	0.540†	0.331
Sig. (2-tailed)		0.000	0.000	0.041	0.014	0.154
N	20	20	20	20	20	20
TSK-13						
Pearson Correlation	0.945*	1	0.972*	0.444†	0.524†	0.326
Sig. (2-tailed)	0.000		0.000	0.050	0.018	0.160
N	20	20	20	20	20	20
TSK-11						
Pearson Correlation	0.959*	0.972*	1	0.518†	0.604*	0.395
Sig. (2-tailed)	0.000	0.000		0.019	0.005	0.085
N	20	20	20	20	20	20
FABQ-total						
Pearson Correlation	0.460†	0.444†	0.518†	1	0.782*	0.954*
Sig. (2-tailed)	0.041	0.050	0.019		0.000	0.000
N	20	20	20	20	20	20
FABQ-activities						
Pearson Correlation	0.540†	0.524†	0.604*	0.782*	1	0.596*
Sig. (2-tailed)	0.014	0.018	0.005	0.000		0.006
N	20	20	20	20	20	20
FABQ-W						
Pearson Correlation	0.331	0.326	0.395	0.954*	0.596*	1
Sig. (2-tailed)	0.154	0.160	0.085	0.000	0.006	
N	20	20	20	20	20	20

* Correlation is significant at the 0.01 level (2-tailed).

† Correlation is significant at the 0.05 level (2-tailed).

Statistically significant results are indicated in bold.

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Appendix A: Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at <http://links.lww.com/PR9/A5>.

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References

- Barke A, Baudewig J, Schmidt-Samoa C, Dechent P, Kröner-Herwig B. Neural correlates of fear of movement in high and low fear-avoidant chronic low back pain patients: an event-related fMRI study. *PAIN* 2012; 153:540–52.
- Bronfort G, Haas M, Evans RL, Bouter LM. Efficacy of spinal manipulation and mobilization for low back pain and neck pain: a systematic review and best evidence synthesis. *Spine J* 2004;4:335–56.
- Diedenhofen B, Musch J. Cocor: a comprehensive solution for the statistical comparison of correlations. *PLoS One* 2015;10: e0121945.
- Ellingsen DM, Wessberg J, Eikemo M, Lijencrantz J, Endestad T, Olsson H, Leknes S. Placebo improves pleasure and pain through opposite modulation of sensory processing. *Proc Natl Acad Sci U S A* 2013;110:17993–8.
- Fields H. State-dependent opioid control of pain. *Nat Rev Neurosci* 2004; 5:565–75.
- Goubert L, Crombez G, van Damme S, Vlaeyen JWS, Bijttebier P, Roelofs J. Confirmatory factor analysis of the Tampa Scale for Kinesiophobia: invariant two-factor model across low back pain patients and fibromyalgia patients. *Clin J Pain* 2004;20:103–10.
- Gravetter F, Wallnau L. *Essentials of statistics for the behavioral sciences*, 8th Edition. Belmont, NY: Wadsworth, 2014.
- Hittner JB, May K, Silver NC. A Monte Carlo evaluation of tests for comparing dependent correlations. *J Gen Psychol* 2003;130:149–68.
- Kober H, Barrett LF, Joseph J, Bliss-Moreau E, Lindquist K, Wager TD. Functional grouping and cortical-subcortical interactions in emotion: a meta-analysis of neuroimaging studies. *NeuroImage* 2008;42: 998–1031.
- Kryklywy JH, Nantes SG, Mitchell DGV. The amygdala encodes level of perceived fear but not emotional ambiguity in visual scenes. *Behav Brain Res* 2013;252:396–404.
- Kuner R. Central mechanisms of pathological pain. *Nat Med* 2010;16: 1258–66.
- Leeuw M, Goossens MEJB, Linton SJ, Crombez G, Boersma K, Vlaeyen JWS. The fear-avoidance model of musculoskeletal pain: current state of scientific evidence. *J Behav Med* 2007;30:77–94.
- Leeuw M, Goossens MEJB, van Breukelen GJP, Boersma K, Vlaeyen JWS. Measuring perceived harmfulness of physical activities in patients with chronic low back pain: the Photograph Series of Daily Activities—short electronic version. *J Pain* 2007;8:840–9.
- Linnman C, Moulton EA, Barmettler G, Becerra L, Borsook D. Neuroimaging of the periaqueductal gray: state of the field. *NeuroImage* 2012;60:505–22.
- McLaren DG, Ries ML, Xu G, Johnson SC. A generalized form of context-dependent psychophysiological interactions (gPPI): a comparison to standard approaches. *NeuroImage* 2012;61:1277–86.
- Meier ML, Stampfli P, Vrana A, Humphreys BK, Seifritz E, Hotz-Boendermaker S. Neural Correlates of Fear of Movement in Patients with Chronic Low Back Pain vs. Pain-Free Individuals. *Front Hum Neurosci* 2016;10:386.
- Mlekusch S, Nezir AY, Limacher A, Juni P, Arendt-Nielsen L, Curatolo M. Conditioned pain modulation in patients with acute and chronic low back pain. *Clin J Pain* 2016;32:116–21.
- O’Reilly JX, Woolrich MW, Behrens TEJ, Smith SM, Johansen-Berg H. Tools of the trade: psychophysiological interactions and functional connectivity. *Soc Cogn Affect Neurosci* 2012;7:604–9.
- Peterson CK, Bolton J, Humphreys BK. Predictors of improvement in patients with acute and chronic low back pain undergoing chiropractic treatment. *J Manipulative Physiol Ther* 2012;35:525–33.
- Price DD, Verne GN, Schwartz JM. Plasticity in brain processing and modulation of pain. *Prog Brain Res* 2006;157:333–52.

- [21] Rapoport J, Jacobs P, Bell NR, Klarenbach S. Refining the measurement of the economic burden of chronic diseases in Canada. *Chronic Dis Can* 2004;25:13–21.
- [22] Rizvi TA, Ennis M, Behbehani MM, Shipley MT. Connections between the central nucleus of the amygdala and the midbrain periaqueductal gray: topography and reciprocity. *J Comp Neurol* 1991;303:121–31.
- [23] Seifritz E, Esposito F, Neuhoff JG, Lüthi A, Mustovic H, Dammann G, von Bardeleben U, Radue EW, Cirillo S, Tedeschi G, Di Salle F. Differential sex-independent amygdala response to infant crying and laughing in parents versus nonparents. *Biol Psychiatry* 2003;54:1367–75.
- [24] Silvers JA, Wager TD, Weber J, Ochsner KN. The neural bases of uninstructed negative emotion modulation. *Social Cogn Affect Neurosci* 2015;10:10–8.
- [25] Staud R. The important role of CNS facilitation and inhibition for chronic pain. *Int J Clin Rheumatol* 2013;8:639–46.
- [26] Tkachuk GA, Harris CA. Psychometric properties of the Tampa Scale for Kinesiophobia-11 (TSK-11). *J Pain* 2012;13:970–7.
- [27] Veinante P, Yalcin I, Barrot M. The amygdala between sensation and affect: a role in pain. *J Mol Psychiatry* 2013;1:9.
- [28] Villemure C, Bushnell MC. Mood influences supraspinal pain processing separately from attention. *J Neurosci* 2009;29:705–15.
- [29] Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *PAIN* 2000;85:317–32.
- [30] Waddell G, Newton M, Henderson I, Somerville D, Main CJ. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. *PAIN* 1993;52:157–68.
- [31] Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science* 2004;303:1162–7.
- [32] Wertli MM, Rasmussen-Barr E, Weiser S, Bachmann LM, Brunner F. The role of fear avoidance beliefs as a prognostic factor for outcome in patients with nonspecific low back pain: a systematic review. *Spine J* 2014;14:816–36.e4.
- [33] Yu R, Gollub RL, Spaeth R, Napadow V, Wasan A, Kong J. Disrupted functional connectivity of the periaqueductal gray in chronic low back pain. *Neuroimage Clin* 2014;6:100–8.