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Investigating behavioral brain system activity on pain intensity, with mediating role of cognitive flexibility in patients with chronic pain

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Abstract
Introduction: This study aimed to assess the activity of the behavioral brain system based on pain intensity with the mediating role of cognitive flexibility in patients with chronic pain.

Materials and Methods: In order to conduct research, 200 patients with various types of chronic pain, who had referred to specialized clinics and offices of neurologists in Zahedan in 2020, were selected through the convenient method. Participants fulfilled the Jackson Questionnaire, the Dennis and Vanderwall Cognitive Flexibility Scale, and Van Korf et al. (1992) Pain Scale. Then, the data were analyzed using path analysis method, based on SPSS22 and AMOS-21 software.

Results: The results show that the dimensions of the behavioral brain system are significantly associated with pain intensity. It had an inverse and significant relationship with the Behavioral Activation System (BAS) and had a positive and significant relationship with the Behavioral Inhibition System (BIS) ($P<0.05$). Cognitive paternal flexibility and pain intensity are also indirectly related to each other; therefore, it can be said that as patients' cognitive flexibility increases, their pain intensity score decreases. Also, this study showed that cognitive flexibility does not play a mediating role between the war components (FFFS) but between the FFS system with intensity pain.

Conclusion: According to the results of the present study, there is a positive and significant relationship between behavioral inhibition system and cognitive flexibility and pain intensity. Also, cognitive flexibility is a mediating variable on the two components of inhibition and fear.

Keywords: Behavioral brain system activity, Chronic pain, Cognitive flexibility, Intensity

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Introduction

Patients with chronic pain suffer from substantial emotional strain and stress and live with diminished emotional strengths. Chronic pain is a type of pain that persists for more than three months, with an estimated rate of 10 to 30% in adults (1). Pain is among the most common causes for seeking intervention from healthcare facilities. It also brings distress and other stressful implications to the family and work hours (2). International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. However, the IASP's definition of pain has undergone several revisions and

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amendments. In the latest revision, Sternke and colleagues redefined pain as a distressing sensory, emotional, cognitive, and social experience associated with actual or potential tissue damage (3). Chronic pain prevalence among Iranian adults aged 18 to 65 has been reported from 9 to 12 percent (4-6).

According to Ardalan and co-workers (7), psychological factors and various emotions are associated with pain persistence and severity. Brain-behavioral systems are extensively investigated in studies on pain severity. According to Jeffrey Gray's Reinforcement Sensitivity Theory (RST; 1970), personality is quite tangled with brain-behavioral systems (8).

Gray's RST theory differentiates three distinct but interacting brain systems to explain personality variations, including the behavioral activation system (BAS), the behavioral inhibition system (BIS), and the fight-flight system (FFS). By definition, individuals with stronger BAS and weaker BIS show more purposeful behaviors and are less prone to elaborate stress when facing and dealing with new and unknown stimuli (9). Research has shown that disability and pain perception differs in various individuals (9,10), with patients with chronic pain who perform their regular tasks and activities (11).

In general, individuals' mental health originates from a two-way interaction between certain types of cognitive emotion regulation strategies and correct assessment of stressful situations. Cognitive emotion regulation strategies help individuals to regulate adverse incidents or traumatic events. They are also directly related to the development, progression, or incidence of psychosomatic disorders such as pain (12). Cognitive flexibility is the ability to switch cognitive sets to adapt to changing environmental stimuli (13). It plays an essential role in coping with chronic pain, in particular (14). Cognitive flexibility plays a determinant role during adaptation. Therefore, it is wise to explore underlying factors contributing to changes in cognitive flexibility in individuals. Acceptance and commitment therapy (ACT) is among the latest theories on flexibility developed by Hayes, Luoma, and co-workers (15). ACT has led to the next generation of therapies. Conscious attention to the present moment and the process of adaptation strengthen committed actions, behavior changes, and psychological flexibility (16). Some theorists consider cognitive flexibility a multifaceted construct incorporating fundamental components, including temperament, personality, and special skills such as problem-solving. Such skills enable individuals when dealing with traumatic events and during adaptation (17).

This component appears in varying degrees in different individuals and leads them to react against new experiences (18). According to Dennis and Vander Wal, cognitive flexibility influences the incidence of damages and the level of social functioning in individuals. They believe that individuals with cognitive flexibility use alternative justifications (18) and show more psychological resilience toward problems than no flexible counterparts (19).

Psychological components are efficient in overcoming implications in patients with chronic pain, given the prevalence of chronic pain and co-movements between functions of brain-behavioral systems and many psychiatric disorders, as established in the literature. Given the above topics, this study explored the relationship between functions of the brain-behavioral system and pain severity in patients with chronic pain with the mediating role of cognitive flexibility.

Materials and Methods

The present work was a descriptive study based on the structural equation modeling (SEM) technique conducted on patients with chronic pain (low back pain, headache, rheumatoid arthritis, osteoarthritis) referred to specialized neurologic clinics and medical facilities in Zahedan from winter 2020 to spring 2021. Invalid questionnaires were excluded, and a total number of 200 patients were ultimately selected through a non-random and convenience sampling method (20).Chronic pain in patients was approved by specialists in which patients enduring pain at least for two days during the two past years, even with painkillers, were diagnosed and included in the study. Notably, IASP has considered chronic pain as a type of pain that persists at least from three to six months (21). Inclusion criteria were: not having neurologic and psychologic disability and disorder and damages to the brain, not having addiction to alcohol and other substances, aged 33-65 years, and having sufficient knowledge to respond to the items in questionnaires

By contrast, patients with hypertension, history of cardiovascular diseases, overweight and obesity, dementia and memory loss (such as Alzheimer's disease), the history of surgery during the past three months, and pregnancy were excluded from the study. Participants were asked to sign the consent form and thoroughly replay all items intended in questionnaires. Patients were also provided with a book on psychological pain management approaches to achieve more practical results. The study was conducted after obtaining permits and a code of ethics and explaining all the ethical principles and the study procedures to the participants. Data were analyzed through path analysis in IBM SPSS Amos-21 and SPSS-22 software (IBM).

Research instruments

A) Jackson's Five-Factor Questionnaire: The Persian version of Jackson's Five-Factor Questionnaire was used to assess the effects of brain-behavioral systems on variables. This scale is a 30-item questionnaire with five subscales designed by Jackson in 2009 as a revised reinforcement sensitivity theory (r-RST) incorporating five subscales of r-BAS, r-BIS, r-Fight, r-Flight, and Freezing. Six items are granted to each r-RST subscale. In Iran, r-RST's Persian version was released by Hasani, Salehi, and Rasooli in 2012, and its psychometric properties were standardized (22).

B) Cognitive Flexibility Index (CFI; Dennis and Vander Wal, 2010): Dennis and Vander Wal first developed the cognitive Flexibility Index (CFI) in 2010 (18). CFI is a 20-item questionnaire designed to assess a person's clinical and non-clinical performance and his or her ability to develop flexible thinking in cognitive behavioral therapy (CBT) of depression and other psychological conditions. In Iran, Share and co-workers (2014) outlined three subscales for CFI, including alternatives, control, and alternatives for human behaviors. CFI is based on a five-point Likert scale with response options ranging from strongly disagree to strongly agree (23). Questions 2, 4, 7, 9, 11, and 17 are scored reversely. CFI's total score is the sum of the scores of all the questions. Likewise, the total score of each subscale is the sum of the scores of the questions of that subscale. Dennis and Vander Wal (2010) reported concurrent validity of - 0.39 for this questionnaire with Beck Depression Inventory (BDI) and convergent validity of 0.75 with the cognitive flexibility scale of Martin and Robin. In Iran, Share and co-workers (2014) reported a full retest coefficient scale of 0.71 and Cronbach's alpha coefficients of the total scale of 0.90 (23). Additionally, the Cronbach's alpha coefficient of the total scale of 0.75 was reported by Fazeli and co-workers in 2014 (24). In this study, Cronbach's alpha for alternatives, control, and alternatives for human behavior was 0.72, 0.55, 0.57, respectively (24).

C) Von Korff's Questionnaire for Grading the Severity of Chronic Pain: Von Korff and co-workers first proposed this scale in 1992 to measure the severity of pain in participants (Smith et al., 1997). The questionnaire covers three dimensions of pain severity, persistence, duration, and associated disabilities. Questions are based on an 11-point scale, with responses ranging from zero to ten. In a 1995 study by Smith and colleagues on 400 patients with chronic pain, the internal reliability and the content validity of all questions were respectively 0.91 and more than 0.75 (25).

Results

Of all the study participants, 24.5% were 21 to 33 years old, 38% were aged 34 to 46 years, and 37.5% were from 47 to 59 years. Likewise, 33.00% of the participants were male, and the remaining 67.00% were female. Furthermore, 38% of participants were married, and 62% were single. Of all respondents, 28% had a BC degree, and 14% were under diploma. Additionally, 28% of patients had a headache, 33% had chronic low back pain, 22% had rheumatoid arthritis, and 17% had osteoarthritis. Patients suffered from chronic pain at least two days a week during the past two years, even with painkillers.

Table 1. Scores of cognitive flexibility, brain-behavioral systems, and pain severity by the mean and standard deviation

Variable	Mean	SD
Perception of alternatives	14.94	3.11
Perception of controllability	23.69	4.93
Perception of behavioral adjustment	3.24	1.12
Total score of cognitive flexibility	40.79	7.32
BAS	20.85	4.22
BIS	21.65	4.93
Fight	16.14	4.40
Flight	16.87	4.24
Freezing	16.88	4.55
Pain severity	58.76	5.89

Table 1 presents scores (by mean and SD) for cognitive flexibility (M=40; SD=7.32), components of the brain-behavioral system, including BFS (M=20.85; SD=4.22), BIS (M=21.65; SD=4.93), fight (M=16.14; SD=4.40), flight (M=16.87; SD=4.24), and freezing (M=16.88; SD=4.55), perception of behavioral adjustment (M=3.24; SD=1.12), and pain severity (M=75; SD=5.89).

Table 2. Direct and indirect BFS-pain severity path analysis results

	Path	β	t-value	SEM; σM	P	Cl
Overall	BAS → pain severity	- 0.203	0.098	- 2.06	0.04	(- 0.008) (- 0.396)
Direct	BAS → pain severity	- 0.213	0.097	- 2.20	0.02	(- 0.022) (- 0.404)
		β	Bootstrap error			Cl
Indirect	BAS → cognitive flexibility → pain severity	0.022	0.0197			(0.068) (- 0.01)

According to Table 2, the overall and direct effect of BAS on pain severity is significant ($P< 0.05$). When cognitive flexibility is included in the path as a mediator, the indirect effect of BAS on pain severity will be significant ($P= 0.022$).

Table 3. Direct and indirect BIS-pain severity path analysis results

	Path	β	t-value	SEM; σM	P	Cl
Overall	BIS → pain severity	- 0.194	0.084	- 2.31	0.02	(- 0.028) (- 0.359)
Direct	BAS → pain severity	- 0.225	0.082	- 2.71	0.007	(- 0.061) (- 0.388)
		β	Bootstrap error			Cl
Indirect	BIS → cognitive flexibility → pain severity	0.031	0.0160			(0.066) (0.004)

According to table 3, BIS's overall and direct effect on pain severity is significant ($P< 0.05$). When cognitive flexibility is included as a mediator in the path, the indirect effect of BIS on pain severity will be significant ($P= 0.031$), indicating the mediatory role of cognitive flexibility between BIS and pain severity.

Table 4. Direct and indirect fight-pain severity path analysis results

	Path	β	t-value	SEM; σM	P	Cl
Overall	Fight → pain severity	0.03	0.093	0.32	0.75	(0.212) (- 0.153)
Direct	Fight → pain severity	- 0.032	0.094	- 0.34	0.736	(0.154) (- 0.217)
		β	Bootstrap error			Cl
Indirect	Fight → cognitive flexibility → pain severity	0.004	0.014			(0.038) (- 0.019)

According to table 4, the overall and direct effect of the fight on pain severity is significant ($P< 0.05$). However, when cognitive flexibility is included as a mediator in the path, the effect of the fight on pain severity will be indirect and significant ($P= 0.004$). Therefore, cognitive flexibility does not mediate the relationship between fight and pain severity.

Table 5. Direct and indirect flight-pain severity path analysis results

	Path	β	t-value	SEM; σM	P	Cl
Overall	Flight → pain severity	0.077	0.092	0.84	0.4	(0.258) (- 0.104)
Direct	Flight → pain severity	0.062	0.092	0.067	0.5	(0.244) (- 0.120)
		β	Bootstrap error			Cl
Indirect	Flight → cognitive flexibility → pain severity	- 0.021	0.018			(0.009) (- 0.061)

According to table 5, the overall and direct effect of flight on pain severity is not significant ($P> 0.05$). However, when cognitive flexibility is included as a mediator in the path, the indirect effect of flight on pain severity will be significant ($P= -0.21$). Therefore, cognitive flexibility mediates the relationship between flight and pain severity.

Table 6. Direct and indirect freezing-pain severity path analysis results

	Path	β	t-value	SEM; σM	P	Cl
Overall	Freezing → pain severity	0.133	0.096	1.382	0.16	(0.323) (- 0.056)
Direct	Freezing → pain severity	0.041	0.106	0.386	0.7	(0.251) (- 0.169)
		β	Bootstrap error			Cl
Indirect	Freezing → cognitive flexibility → pain severity	- 0.002	0.017			(0.381) (- 0.033)

According to Table 6, the overall and direct effect on pain severity is not significant (*P*> 0.05). Furthermore, even with cognitive flexibility as a mediator in the path, the indirect effect of freezing on pain severity will not be significant (*P*= -0.002), indicating the mediatory role of cognitive flexibility between freezing and pain severity.

Discussion

This study investigated the activity of the brain-behavioral system on pain severity with the mediating role of cognitive flexibility in patients with chronic pain. Dimensions of the brain-behavioral system were significantly correlated to pain severity. There was a negative and significant relationship between BAS and pain severity, in agreement with the results reported with Amiri, Gary, Badihi, and Pahlavan (4,10,11,16). By contrast, a significant and positive relationship was observed between BIS and pain severity, similar to the results reported by Pahlavan, Stranke, and Degna et al. (3,14,26). Furthermore, a negative and significant correlation was found between FFS and pain severity, as similarly reported by Hayes et al., Banaian et al., and Gary et al. (9,12,15). Pahlavan and colleagues studied the mediatory role of BIS in 448 patients with chronic pain to predict the pain severity based on emotional alexithymia. They found a significant and positive relationship between pain severity and BIS and FFS at the significant levels of 0.01 and 0.05, respectively (26). In a similar study, BAS and BIS functions and the mediatory role of cognitive flexibility were compared in 30 women with substance use disorders and healthy participants. A significant difference was observed in BAS functions between the two groups, with higher BAS scores found in women with substance use disorders (27). This finding can be explained by Gray's theory (Gray, 1990). The advent of Jeffrey Gray's theory (1981-1987) has enabled explaining many findings during the past two decades. Gray's theory evaluates diseases from a psychophysiological perspective (8). Many studies attempt to explore relationships between components of the brain-behavior system, the mediatory role of cognitive flexibility, and pain severity. Similar to the present study, some studies have explored the relationship between brain-behavioral systems to explain physical disorders. Gray attributed the response of individuals to environmental stimuli to neurological BAS and BIS systems (17). Variations and disturbances in the activity of BAS and BIS systems are associated with various psychiatric and psychosomatic disorders (9). Additionally, cognitive flexibility was mediating between brain-behavioral systems and the pain severity perceived in patients with chronic pain. This confirms one of the hypotheses raised in this research, in agreement with the results reported by Share et al., Fazeli et al., and Phamt Pel et al. (19,23,24). Investigation of pain severity in 4645 Swedish patients with chronic pain revealed considerable variation among symptoms such as pain, depression, and anxiety, with 60% of pain severity that was primarily caused due to psychological factors (28). Similar to the results of our study, Mint et al. investigated the effects of psychosocial participation on chronic pain and found that the pain's biopsychosocial model affects the perception of chronic pain among academic communities.

The study of mental distress, trauma, and interpersonal factors showed that psychological factors influence the persistence of chronic pain, and pain severity is higher in patients with trauma or lower psychological tolerance and more anxiety (29). Effects of mindfulness, psychological flexibility, and coherent self-knowledge were studied on psychological well-being in 410 students at Kashan University of Medical Sciences (Kashan, Iran). There was a positive and significant correlation between psychological flexibility and psychological well-being. Mindfulness, psychological flexibility, and coherent self-knowledge significantly explained the large portion of psychological well-being dispersions for more simplicity (30). Pain can be the most prevalent and inevitable manifestation of mental pressures. For pain alleviation, patients with chronic pain need medical interventions and psychological supports, which are achieved by some techniques such as cognitive flexibility. By definition, cognitive flexibility is the ability to reorganize and use data in response to various situations (24). Many studies support the reduced pain and pain adjustment in patients with higher flexibility (11,22,25). Individuals with no cognitive flexibility are not adaptable when facing environmental and social changes and tend to arrange all affairs the same way (26). Cognitive flexibility can affect the functions of brain-behavioral systems and the associated components (e.g., BAS, BIA, FFS, FFFS) so that pain is more severely perceived with the BIA component (31). By contrast, cognitive flexibility shows a negative effect on functions of the BAS, i.e., higher cognitive flexibility enhances the BAS's activity and consequently reduces pain severity (14,19,32). Our results, with that of the previous studies, show that psychological factors such as flexibility and resilience are effective in pain alleviation (9,29,33), and brain-behavioral systems, originated from personality theories, might play a critical role in this flexibility and adaptation to pain (8, 24).

Limitations of our study were covering only patients with chronic pain referred to neurologic clinics in Zahedan, restrictions imposed by the Covid-19 pandemic, and invalid and non-completed questionnaires. Importantly, in studies in which data are gathered through self-reporting by participants, the accuracy and transparency of responses can be primarily suspected.

Conclusion

The findings support the critical role of physical parameters and psychological factors in the incidence or worsening of various types of pain. In general, individuals with stronger cognitive flexibility suffer less from chronic pain. In addition to cognitive flexibility, any other psychological factor and diminished anxiety can efficiently alleviate chronic pain in patients.

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