科技部補助專題研究計畫報告

慢性疼痛造成認知功能衰退之性別差異評估：以慢性肩關節疼痛為例 (L03)

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本研究具有政策應用參考價值：■否 □是，建議提供機關
（勾選「是」者，請列舉建議可提供施政參考之業務主管機關）
本研究具影響公共利益之重大發現：□否 □是

中 華 民 國 110 年 10 月 31 日

中 文 摘 要 ： 慢性疼痛的定義為疼痛持續3個月以上。據估計, 全世界約有四分之一的人口受到 慢性疼痛的影響。從大型的流行病學調查中發現，女性受到慢性疼痛的影響較男性 多。目前有越來越多的證據顯示，慢性疼痛會改變大腦迴路，包括灰質減少，白質完整性變差等。同時也反映在認知功能衰退上，包括注意力，記憶力，處理速度 ，執行控制功能，決策能力等。雖然已有相當多的證據顯示疼痛有性別差異，以及 疼痛會造成認知功能衰退，但是目前對於疼痛所造成的認知功能衰退，是否有性別 上的差異仍不清楚。本研究共收集200位肩關節疼痛患者，如同過去的研究一樣，女性通常有較高程度的疼痛、肩功能退化、以及生活品質低落。更有趣的是我們發現疼痛患者的認知測驗上，竟也有性別差異。不過此認知的性別差異，在我們控制教育程度後，發現僅有低教育組別仍可看到認知測驗上的性別差異。

中 文 關 鍵 詞 ： 慢性肩關節疼痛、性別差異、認知退化

英 文 摘 要 ： Chronic pain is defined as pain persisting for at least 3 months, affecting one- quarter of the world’s population. Of interest, women are greatly overrepresented among patients with chronic pain syndromes in large epidemiological studies. Accumulating neuroanatomy evidence has demonstrated that patients with chronic pain showed grey matter loss as well as the impaired white matter integrity within regions involved in cognitive and emotional modulation of pain. Along with the structural changes, chronic pain also causes the deteriorated cognitive function, including attention, memory, psychomotor speed, executive functions, and decision-making. How the sex disparity in chronic pain as well as the cognitive impairment in chronic pain have been well documented, but, to our knowledge, it is unclear whether the sex disparities in chronic pain will deteriorate cognitive functions differently between women and men. We have collected 200 shoulder pain patients. Similar to previous findings, women showed higher pain, lower QOL and shoulder function. Interestingly, there was sex-disparity in cognitive performance, in which women are generally worse than men. Nevertheless, education did confound with cognitive performance. Thus, we further separated participants into lower and higher education group. After controlling for the education, the sex disparity upon cognitive performance was only evident in low education group, but not the higher education group.

英 文 關 鍵 詞 ： chronic shoulder pain, sex difference, sex disparity, cognitive decline

Introduction

Chronic Shoulder Pain

Shoulder pain is the third space of most common musculoskeletal condition(Klintberg et al., 2015). Rotator cuff disorder is the leading cause to shoulder pain among the four common conditions, including rotator cuff disorder, adhesive capsulitis, shoulder arthritis and instability(DanielleAW M vanderWindt, 1995; Greenberg, 2014; Kelton M. BurBanK & J. HerBert StevenSon, 2008; Ostor, Richards, Prevost, Speed, & Hazleman, 2005). Incidence rate of shoulder pain is 11.2/1000/year(DanielleAW M vanderWindt, 1995). The greatest proportion of shoulder pain is recorded as fifth to seventh decades with the peaked age of consulting around fifty years old(DanielleAW M vanderWindt, 1995; Linsell et al., 2006). What's more, incidence of shoulder pain on women is mild greater than men(Bodin et al., 2018; Parsons et al., 2007; Treaster & Burr, 2004).

However, there are still 46% patients complaining about discomfort after 26 months of first consultation, while only 50% of new episode of shoulder pain recover within 6 months and only 18% without chronic episodes(Kuijpers, van Tulder, van der Heijden, Bouter, & van der Windt, 2006; Masters & Burley, 2007; Parsons et al., 2007). Chronic shoulder pain is defined as pain that has persisted more than six months, regardless of previous treatment(Kelton M. BurBanK & J. HerBert StevenSon, 2008). It appears that approximately 20-33% of general population have chronic shoulder pain(McBeth & Jones, 2007). There are some risk factors associated with chronic shoulder pain, including age, gender, work organization, psychosocial and physical problems(Bodin et al., 2018; McBeth & Jones, 2007).

Moreover, shoulder pain becomes a concerning problem not only for economic burden but affects significantly to daily life and activity of patients(Greenberg, 2014). Cost burden of society for shoulder pain was AU$20.72 for non-walkers, while up to AU$61.31 for workers per day(Marks, Comans, Bisset, Thomas, & Scuffham, 2019). Around half of total cost during 6 months after first consultation for shoulder pain is productivity loss(Kuijpers et al., 2006).

Sex differences in clinical pain

Women has higher prevalence of musculoskeletal pain and greatly outnumbers of chronic pain than men(Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Leresche, 2011). Also, women are more sensitive to pain, with higher discrimination ability for varying level of pain, lower threshold and tolerance to pain than men, which may be affected by biological, psychological and sociocultural factors(Adrian J Maurer1 & Management, 2016; Bartley & Fillingim, 2013; Mogil, 2012; Totsch, 2017). There are some hypotheses playing important role to pain perception and modulation between women and men, including hormonal level, immune system and different evolutional pattern(Adrian J Maurer1 & Management, 2016; Mogil, 2012; Totsch, 2017). Women with higher estrogen but lower testosterone level can lead to higher level of IFN-γ, which activates Th1 to mediate pain sensation, while men is

opposite(Totsch, 2017). Higher sensitivity of women is not only limited to pain, but multisensory sexual differences and women reveal greater sensitivity detection in many sensory modalities (Hashmi & Davis, 2014).
For shoulder pathology, gender and age are important in quality of life and clinical course of disease(Razmjou, Holtby, & Myhr, 2006). Moreover, women with chronic shoulder injury tend to have higher level of disability and dissatisfaction than men(Razmjou, Davis, Jaglal, Holtby, & Richards, 2011).

Chronic pain and cognition

Chronic pain is a common problem that can widespread affect our daily life, including economic, social status, psychological and general health(Breivik et al., 2006; Elliott, Smith, Penny, Cairns Smith, & Alastair Chambers, 1999; Hooten, 2016). Chronic pain also plays an important role in affecting our brain activity, including memory function, learning, response inhibition, emotion and executive function(Apkarian, Hashmi, & Baliki, 2011; Berryman et al., 2014; Berryman et al., 2013). Fear and depression about the pain should significantly mediate the relationship between pain and disability(Marshall, Schabrun, & Knox, 2017). Furthermore, higher pain rating contributed to the poor sleep quality, while poor prior night sleep predicted the high pain, negative mood and low function across the next day(Blake et al., 2016; Cheatle et al., 2016; Gerhart et al., 2017). According to previous literature, sexual difference on cognition is mainly on spatial performance, sensation seeking and physical aggression(Hyde, 2014). Though there is difference among gender on cognition, it's unclear that whether higher level of chronic shoulder pain has poorer cognition.

Purpose of this study

How the sex difference in chronic pain as well as the cognitive impairment in chronic pain have been well documented, but, to our knowledge, it is unclear whether the sex disparities in chronic pain will deteriorate cognitive functions differently between women and men. Thus, it is warranted to examine multiple cognitive domains in a more delicate way to establish a standard array of cognitive impairments for addressing sex differences in chronic pain populations.

Method

General human participant recruitment: we recruited 200 shoulder pain subjects(men:76; women: 124) from orthopedic (co PI, Dr. Chih-Hao Chiu) based on the following inclusion and exclusion criteria.-All participants will be right-handed adults with normal or corrected-to-normal vision and had no prior history of hearing, reading, psychiatric or neurological disorders, presence or history of neurological stroke, cancer, uncontrolled hypertension, and diabetes.

Inclusion criteria for rotator cuff injury and frozen shoulder：

a. Rotator cuff injury and/or frozen shoulder based on clinical diagnosis by Dr. Chih-Hao Chiu
b. Pain lasts at least for 3 months
c. Patients are willing to enroll either surgery or rehabilitation program

Exclusion criteria

a. Inflammatory joint disease
b. Symptomatic arthritis of the acromioclavicular joint
c. Pathological abnormalities of the subscapularis tendon
d. Workers' compensation claims
e. Prior surgery on the affected shoulders
f. Neurological disease, i.e., stroke, parkinson's disease, etc..
g. Psychiatric disease, i.e., dementia, depression, schizophrenia, etc..
h. Cancer.

Outcome measurements

Pain

As part of the participant screening, participants will be required to state whether they do or do not have a history of chronic shoulder pain. Overall Visual Analog Scale (VAS) for pain will be assessed. VAS ranges from 0 to 100. The higher level of the score is, the higher pain level the patients feel.

Shoulder function evaluation

To assess the shoulder function, Constant-Murley score (CMS)(Constant & Murley, 1987), American Shoulder and Elbow Surgeons Standardized Shoulder Assessment (ASES) (Knaut, Moser, Melo Sde, & Richards, 2010; Piitulainen, Paloneva, Ylinen, Kautiainen, & Hakkinen, 2014; Richards et al., 1994), Global rating of change scores, GRoC(Kamper, Maher, & Mackay, 2009)) , rotator-cuff quality of life(RC-QOL) (Eubank, Mohtadi, Lafave, Wiley, & Emery, 2017), and Western Ontario Rotator Cuff Index (WORC) (Kirkley, Alvarez, & Griffin, 2003) will be evaluated.

CMS is a 100-points scale, which defines the shoulder function by different parameters including subjective pain and objective measurement(Constant & Murley, 1987). Points above 30 reveal poor function of the shoulder. ASES is a 100-point scale to determine functional limitation and pain of shoulder (Knaut et al., 2010; Piitulainen et al., 2014; Richards et al., 1994). The higher of ASES, the better condition of the shoulder function is. RC-QOL represents the quality level of rotator cuff injury(Eubank et al., 2017). Score 0 means the worst of life quality, while score 100 reveals the best quality of life. WORC is a shoulder specific quality of life measurement(Kirkley et al., 2003). However, in contrast to RC-QOL, score 0 indicates no impact on quality of life and score 100 indicates the worst life quality.

Sleep related measurement

Subjective sleep quality Pittsburgh sleep quality index, PSQI (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989)) and Epworth sleepiness scale (ESS) (Johns, 1991)) will be evaluated. PSQI ranges from 0 to 21, when PSQI is more than 5, which indicates the sleep quality disorder. The higher of PSQI is, the poor the sleeping quality is. ESS is used to evaluate daytime sleepiness, from 0 to 24. More than 10 points reveals at least mild excessive daytime sleepiness. The higher of ESS also indicates more serious daytime sleepiness.

Neuropsychological assessments, demographic questionnaires, and health-related measures.

To assess cognitive ability and background information for each participant, we will implement neuropsychological and cognitive testing battery established in the present series of experiments. Details on socioeconomic status, education, employment, daily activity, will be recorded using our comprehensive demographic questionnaire. Also, health-related questionnaires will be acquired, including Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). All these neuropsychological tests will be tested.

MMSE is to measure cognitive measurement, from 0 to 30(Oudman et al., 2014). Cognitive impairment is indicated when less than 24, which will be divided into mild (19~23), moderate (10~18), severe (0~17). MoCA is used to detecting cognitive impairment for dementia, ranging from 0 to 30(Oudman et al., 2014). More than 25 point indicates normal cognitive function, while mild (18~25), moderate (10~17), severe (less than 10) level of cognitive impairment are defined. AD8 is used on assessing early dementia, ranging from 0 to 8. More than 1 point indicates cognitive impairment. BDI is to evaluate depression, ranging from 0 to 63(Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). More than 13 indicates depression, which can be divided into mild (14~19), moderate (20~28), severe (29~63). STAI ranges from 20 to 80, which is used to assess anxiety (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Different level of STAI, including no or low (20~37), moderate (38~44), high (45~80) anxiety are defined. Time duration of Trail Making test is used to assess attention. Digit Span test is to evaluate working memory (WMS-IV) (D. Wechsler, 1997). The higher of the score indicates better working memory. Digit Symbol Substitution Test is for cognitive functioning (Amodio et al., 2002). The higher level of the score indicates the better cognitive function.

Result

As demonstrated in Table 1, there were significant sex differences upon VAS, QOL, shoulder function (ASES), emotional distress (BSI), self-reported sleep quality (PSQI) as well as all the cognitive performances. All the sex difference revealed that women were more vulnerable to the shoulder pain as reflecting on almost dimensions. However, education might be the confounding factors when we consider to compare sex difference upon cognitive

performance. That is, the sex disparity in cognitive function might be related to education per se. Thus, we further separated all the participants into low education level (<=9) (Table 2) and high education level (>9) (Table 3). Interestingly, there was no sex difference among cognitive performance in higher education level, but not the lower education level.

Discussion

In our study, we explored whether sex differences in the chronic shoulder pain would further correlate with emotion, well-being, and cognitive functions. We replicated previous findings by showing women suffered more pain and disability, and have worse quality of life than men. Also, we demonstrated such sex-disparity in pain may further correlate with the deteriorated cognitive function. That is, women showed more cognitive decline than men. However, the cognitive performance was related to education, in which women did get less education resources. Thus, we split groups into lower education and higher education levels. It is interesting to note that the sex differences in cognitive function was not observed in higher education group, while there were still significant difference between men and women.

Even the objective shoulder function score (Constant score) did not reveal any sex difference, women tended to report higher VAS scales, more affected QOL, less sleep quality, as well as the deteriorated cognitive functions. It is interesting to note that the sex-disparity was only evident in lower education level, but not higher education level. It seems education might play as the protective factor. Such argument is also in line with a very recent cohort study that education might be the protective factor when one is getting old (Bloomberg et al., 2021)

Conclusions

In summary, we are the first study to demonstrated the sex disparity in cognitive performance following the chronic shoulder pain. It is interesting that the subjective pain level, regardless of the objective shoulder function, might play an important role in not only the quality of life but also the cognitive performance in those individuals with lower education levels.

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108年度專題研究計畫成果彙整表

計畫主持人：陳柏伃	**計畫編號：**108-2629-H-182-001-
計畫名稱：慢性疼痛造成認知功能衰退之性別差異評估：以慢性肩關節疼痛為例（L03）	

成果項目			量化	單位	質化 （說明：各成果項目請附佐證資料或細項說明，如期刊名稱、年份、卷期、起訖頁數、證號...等）
國內	學術性論文	期刊論文	0	篇	
		研討會論文	1		蔡凱翔、邱致皓、陳柏伃(2020)。慢性肩關節疼痛的性別差異。骨科醫學會學術研討會。 秋季骨科
		專書	0	本	
		專書論文	0	章	
		技術報告	0	篇	
		其他	0	篇	
國外	學術性論文	期刊論文	0	篇	
		研討會論文	0		
		專書	0	本	
		專書論文	0	章	
		技術報告	0	篇	
		其他	0	篇	
參與計畫人力	本國籍	大專生	3	人次	一人以本研究資料投稿，另兩人參與本研究計劃案的文獻閱讀。
		碩士生	0		
		博士生	0		
		博士級研究人員	0		
		專任人員	0		
	非本國籍	大專生	0		
		碩士生	0		
		博士生	0		
		博士級研究人員	0		
		專任人員	0		
其他成果 （無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。）			資料已收集完畢，正在撰寫論文以投稿		

Introduction

Chronic Shoulder Pain

Shoulder pain is the third space of most common musculoskeletal condition(Klintberg et al., 2015). Rotator cuff disorder is the leading cause to shoulder pain among the four common conditions, including rotator cuff disorder, adhesive capsulitis, shoulder arthritis and instability(DanielleAW M vanderWindt, 1995; Greenberg, 2014; Kelton M. BurBanK & J. HerBert StevenSon, 2008; Ostor, Richards, Prevost, Speed, & Hazleman, 2005). Incidence rate of shoulder pain is 11.2/1000/year(DanielleAW M vanderWindt, 1995). The greatest proportion of shoulder pain is recorded as fifth to seventh decades with the peaked age of consulting around fifty years old(DanielleAW M vanderWindt, 1995; Linsell et al., 2006). What's more, incidence of shoulder pain on women is mild greater than men(Bodin et al., 2018; Parsons et al., 2007; Treaster & Burr, 2004).

However, there are still 46% patients complaining about discomfort after 26 months of first consultation, while only 50% of new episode of shoulder pain recover within 6 months and only 18% without chronic episodes(Kuijpers, van Tulder, van der Heijden, Bouter, & van der Windt, 2006; Masters & Burley, 2007; Parsons et al., 2007). Chronic shoulder pain is defined as pain that has persisted more than six months, regardless of previous treatment(Kelton M. BurBanK & J. HerBert StevenSon, 2008). It appears that approximately 20-33% of general population have chronic shoulder pain(McBeth & Jones, 2007). There are some risk factors associated with chronic shoulder pain, including age, gender, work organization, psychosocial and physical problems(Bodin et al., 2018; McBeth & Jones, 2007).

Moreover, shoulder pain becomes a concerning problem not only for economic burden but affects significantly to daily life and activity of patients(Greenberg, 2014). Cost burden of society for shoulder pain was AU$20.72 for non-walkers, while up to AU$61.31 for workers per day(Marks, Comans, Bisset, Thomas, & Scuffham, 2019). Around half of total cost during 6 months after first consultation for shoulder pain is productivity loss(Kuijpers et al., 2006).

Sex differences in clinical pain

Women has higher prevalence of musculoskeletal pain and greatly outnumbers of chronic pain than men(Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006; Leresche, 2011). Also, women are more sensitive to pain, with higher discrimination ability for varying level of pain, lower threshold and tolerance to pain than men, which may be affected by biological, psychological and sociocultural factors(Adrian J Maurer1 & Management, 2016; Bartley & Fillingim, 2013; Mogil, 2012; Totsch, 2017). There are some hypotheses playing important role to pain perception and modulation between women and men, including hormonal level,

immune system and different evolutional pattern(Adrian J Maurer1 & Management, 2016; Mogil, 2012; Totsch, 2017). Women with higher estrogen but lower testosterone level can lead to higher level of IFN-γ, which activates Th1 to mediate pain sensation, while men is opposite(Totsch, 2017). Higher sensitivity of women is not only limited to pain, but multisensory sexual differences and women reveal greater sensitivity detection in many sensory modalities (Hashmi & Davis, 2014).

For shoulder pathology, gender and age are important in quality of life and clinical course of disease(Razmjou, Holtby, & Myhr, 2006). Moreover, women with chronic shoulder injury tend to have higher level of disability and dissatisfaction than men(Razmjou, Davis, Jaglal, Holtby, & Richards, 2011).

Chronic pain and cognition

Chronic pain is a common problem that can widespread affect our daily life, including economic, social status, psychological and general health(Breivik et al., 2006; Elliott, Smith, Penny, Cairns Smith, & Alastair Chambers, 1999; Hooten, 2016). Chronic pain also plays an important role in affecting our brain activity, including memory function, learning, response inhibition, emotion and executive function(Apkarian, Hashmi, & Baliki, 2011; Berryman et al., 2014; Berryman et al., 2013). Fear and depression about the pain should significantly mediate the relationship between pain and disability(Marshall, Schabrun, & Knox, 2017). Furthermore, higher pain rating contributed to the poor sleep quality, while poor prior night sleep predicted the high pain, negative mood and low function across the next day(Blake et al., 2016; Cheatle et al., 2016; Gerhart et al., 2017). According to previous literature, sexual difference on cognition is mainly on spatial performance, sensation seeking and physical aggression(Hyde, 2014). Though there is difference among gender on cognition, it's unclear that whether higher level of chronic shoulder pain has poorer cognition.

Purpose of this study

How the sex difference in chronic pain as well as the cognitive impairment in chronic pain have been well documented, but, to our knowledge, it is unclear whether the sex disparities in chronic pain will deteriorate cognitive functions differently between women and men. Thus, it is warranted to examine multiple cognitive domains in a more delicate way to establish a standard array of cognitive impairments for addressing sex differences in chronic pain populations.

Method

General human participant recruitment: we recruited 200 shoulder pain subjects(men:76; women: 124) from orthopedic (co PI, Dr. Chih-Hao Chiu) based on the following inclusion

and exclusion criteria.-All participants will be right-handed adults with normal or corrected-to-normal vision and had no prior history of hearing, reading, psychiatric or neurological disorders, presence or history of neurological stroke, cancer, uncontrolled hypertension, and diabetes.

Inclusion criteria for rotator cuff injury and frozen shoulder：

a. Rotator cuff injury and/or frozen shoulder based on clinical diagnosis by Dr. Chih-Hao Chiu
b. Pain lasts at least for 3 months
c. Patients are willing to enroll either surgery or rehabilitation program

Exclusion criteria

a. Inflammatory joint disease
b. Symptomatic arthritis of the acromioclavicular joint
c. Pathological abnormalities of the subscapularis tendon
d. Workers' compensation claims
e. Prior surgery on the affected shoulders
f. Neurological disease, i.e., stroke, parkinson's disease, etc..
g. Psychiatric disease, i.e., dementia, depression, schizophrenia, etc..
h. Cancer.

Outcome measurements

Pain

As part of the participant screening, participants will be required to state whether they do or do not have a history of chronic shoulder pain. Overall Visual Analog Scale (VAS) for pain will be assessed. VAS ranges from 0 to 100. The higher level of the score is, the higher pain level the patients feel.

Shoulder function evaluation

To assess the shoulder function, Constant-Murley score (CMS)(Constant & Murley, 1987), American Shoulder and Elbow Surgeons Standardized Shoulder Assessment (ASES) (Knaut, Moser, Melo Sde, & Richards, 2010; Piitulainen, Paloneva, Ylinen, Kautiainen, & Hakkinen, 2014; Richards et al., 1994), Global rating of change scores, GRoC(Kamper, Maher, & Mackay, 2009)) , rotator-cuff quality of life(RC-QOL) (Eubank, Mohtadi, Lafave, Wiley, & Emery, 2017), and Western Ontario Rotator Cuff Index (WORC) (Kirkley, Alvarez, & Griffin, 2003) will be evaluated.

CMS is a 100-points scale, which defines the shoulder function by different parameters including subjective pain and objective measurement(Constant & Murley, 1987). Points above 30 reveal poor function of the shoulder. ASES is a 100-point scale to determine functional limitation and pain of shoulder (Knaut et al., 2010; Piitulainen et al., 2014; Richards et al., 1994). The higher of ASES, the better condition of the shoulder function is.

RC-QOL represents the quality level of rotator cuff injury(Eubank et al., 2017). Score 0 means the worst of life quality, while score 100 reveals the best quality of life. WORC is a shoulder specific quality of life measurement(Kirkley et al., 2003). However, in contrast to RC-QOL, score 0 indicates no impact on quality of life and score 100 indicates the worst life quality.

Sleep related measurement

Subjective sleep quality Pittsburgh sleep quality index, PSQI (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989)) and Epworth sleepiness scale (ESS) (Johns, 1991)) will be evaluated. PSQI ranges from 0 to 21, when PSQI is more than 5, which indicates the sleep quality disorder. The higher of PSQI is, the poor the sleeping quality is. ESS is used to evaluate daytime sleepiness, from 0 to 24. More than 10 points reveals at least mild excessive daytime sleepiness. The higher of ESS also indicates more serious daytime sleepiness.

Neuropsychological assessments, demographic questionnaires, and health-related measures.

To assess cognitive ability and background information for each participant, we will implement neuropsychological and cognitive testing battery established in the present series of experiments. Details on socioeconomic status, education, employment, daily activity, will be recorded using our comprehensive demographic questionnaire. Also, health-related questionnaires will be acquired, including Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). All these neuropsychological tests will be tested.

MMSE is to measure cognitive measurement, from 0 to 30(Oudman et al., 2014). Cognitive impairment is indicated when less than 24, which will be divided into mild (19~23), moderate (10~18), severe (0~17). MoCA is used to detecting cognitive impairment for dementia, ranging from 0 to 30(Oudman et al., 2014). More than 25 point indicates normal cognitive function, while mild (18~25), moderate (10~17), severe (less than 10) level of cognitive impairment are defined. AD8 is used on assessing early dementia, ranging from 0 to 8. More than 1 point indicates cognitive impairment. BDI is to evaluate depression, ranging from 0 to 63(Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). More than 13 indicates depression, which can be divided into mild (14~19), moderate (20~28), severe (29~63). STAI ranges from 20 to 80, which is used to assess anxiety (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). Different level of STAI, including no or low (20~37), moderate (38~44), high (45~80) anxiety are defined. Time duration of Trail Making test is used to assess attention. Digit Span test is to evaluate working memory (WMS-IV) (D. Wechsler, 1997). The higher of the score indicates better working memory. Digit Symbol

Substitution Test is for cognitive functioning (Amodio et al., 2002). The higher level of the score indicates the better cognitive function.

Result

As demonstrated in Table 1, there were significant sex differences upon VAS, QOL, shoulder function (ASES), emotional distress (BSI), self-reported sleep quality (PSQI) as well as all the cognitive performances. All the sex difference revealed that women were more vulnerable to the shoulder pain as reflecting on almost dimensions. However, education might be the confounding factors when we consider to compare sex difference upon cognitive performance. That is, the sex disparity in cognitive function might be related to education per se. Thus, we further separated all the participants into low education level (<=9) (Table 2) and high education level (>9) (Table 3). Interestingly, there was no sex difference among cognitive performance in higher education level, but not the lower education level.

Table 1. Welch t test for contrasting sex difference.

	Men			women			
group	N	Mean	SD	N	Mean	SD	p value
age	76	58.36	11.61	124	61.40	9.43	0.056
education (year)	76	10.91	4.33	124	9.00	4.71	0.004*
pain duration(month)	73	25.00	39.12	120	17.53	31.16	0.168
muscle quality	71	0.79	1.11	119	0.82	1.12	0.874
Pre Constant	73	47.62	10.46	118	45.21	12.30	0.151
VAS	76	60.52	21.67	124	73.52	22.06	0*
RC_QOL	73	49.94	18.52	117	38.05	20.78	0*
BDI	76	8.27	7.83	124	10.94	9.19	0.029*
PSQI	76	7.12	3.61	124	8.43	4.03	0.018*
STAI_S	76	31.17	12.74	124	33.92	13.32	0.145
STAI_T	76	33.36	11.58	124	35.23	14.12	0.308
MMSE	66	27.47	2.14	102	26.28	4.39	0.021*
MOCA	66	23.97	3.56	99	21.98	4.94	0.003*
DigitSpan	45	26.84	7.10	83	23.87	6.20	0.02*
DigitSymbol	65	59.14	20.66	98	50.61	21.70	0.013*

Welch t test was conducted given on the unequal sample size (and unequal variance) between men and women.

Table 2 Welch t test for contrasting sex difference in subgroups of lower education level (as we defined as <= 9, which account for almost 50% patients)

	Men			women			
education <= 9	N	Mean	SD	N	Mean	SD	p value
age	29	64.41	9.12	69	66.304	6.438	0.316
education (year)	29	6.38	2.92	70	5.543	2.842	0.197
pain duration(month)	27	22.53	41.56	68	20.857	35.855	0.855
muscle quality	27	1.00	1.33	68	1.130	1.196	0.655
Pre Constant	26	46.46	11.76	66	43.150	12.050	0.233
VAS	29	64.31	21.58	70	77.071	22.754	0.011
RC_QOL	26	45.17	20.81	68	36.499	21.462	0.080
BDI	29	6.79	8.40	70	11.800	10.389	0.015
PSQI	29	7.34	4.13	70	8.900	4.087	0.093
STAI_S	29	28.69	11.60	70	34.286	14.019	0.044
STAI_T	29	31.24	11.41	70	36.243	15.022	0.076
MMSE	23	26.09	2.37	57	24.649	5.163	0.093
MOCA	23	22.39	3.88	54	19.907	5.217	0.025
DigitSpan	12	21.33	7.45	45	21.510	5.607	0.940
DigitSymbol	23	43.96	16.79	53	37.642	16.062	0.135

Table 3 Welch t test for contrasting sex difference in subgroups of lower education level (as we defined as <= 9, which account for almost 50% patients)

	Men			women			
education >9	N	Mean	SD	N	Mean	SD	p value
age	47	54.62	11.48	54	55.37	9.03	0.72
education	48	13.65	2.21	54	13.47	2.17	0.69
pain duration	46	26.45	38.01	51	13.37	23.48	0.05
muscle quality	44	0.66	0.94	50	0.40	0.86	0.17
Pre Constant	47	48.26	9.74	51	48.10	12.18	0.94
VAS	48	58.23	21.62	54	68.43	20.21	0.02
RC_QOL	47	52.59	16.77	48	40.66	19.75	0.00
BDI	48	9.17	7.42	54	9.93	7.39	0.61
PSQI	47	6.98	3.28	53	7.83	3.96	0.24
STAI_S	48	32.67	13.27	53	33.58	12.54	0.72
STAI_T	48	34.65	11.62	53	34.09	12.93	0.82
MMSE	43	28.21	1.58	45	28.36	1.54	0.66
MOCA	43	24.81	3.10	45	24.47	3.14	0.60
DigitSpan	33	28.85	5.90	38	26.66	5.74	0.12
DigitSymbol	42	67.45	17.75	45	65.89	17.09	0.68

Discussion

In our study, we explored whether sex differences in the chronic shoulder pain would further correlate with emotion, well-being, and cognitive functions. We replicated previous findings by showing women suffered more pain and disability, and have worse quality of life than men. Also, we demonstrated such sex-disparity in pain may further correlate with the deteriorated cognitive function. That is, women showed more cognitive decline than men. However, the cognitive performance was related to education, in which women did get less education resources. Thus, we split groups into lower education and higher education levels. It is interesting to note that the sex differences in cognitive function was not observed in higher education group, while there were still significant difference between men and women.

Even the objective shoulder function score (Constant score) did not reveal any sex difference, women tended to report higher VAS scales, more affected QOL, less sleep quality, as well as the deteriorated cognitive functions. It is interesting to note that the sex-disparity was only evident in lower education level, but not higher education level. It seems education might play as the protective factor. Such argument is also in line with a very recent cohort study that education might be the protective factor when one is getting old (Bloomberg et al., 2021)

Conclusions

In summary, we are the first study to demonstrated the sex disparity in cognitive performance following the chronic shoulder pain. It is interesting that the subjective pain level, regardless of the objective shoulder function, might play an important role in not only the quality of life but also the cognitive performance in those individuals with lower education levels.

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