科技部補助專題研究計畫成果報告
期末報告

經前不悅症之易怒機轉：情緒易感受性、情緒管理、與認知控制(重點代號:GM08)

計 畫 類 別 ：個別型計畫
計 畫 編 號 ：NSC 102-2629-B-037-001-
執 行 期 間 ：102 年 08 月 01 日至 103 年 07 月 31 日
執 行 單 位 ：高雄醫學大學醫學系精神科

計 畫 主 持 人：柯志鴻
共 同 主 持 人：劉金昌、顏如佑、龍震宇
計畫參與人員：學士級-專任助理人員：梁智媛

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3.「本報告」是否建議提供政府單位施政參考：否

中 華 民 國 103 年 10 月 29 日

中文摘要：經前不悅症係指育齡之婦女在月經來潮之前一週，會出現顯著的情緒，認知，與行為上的變化。其症狀顯著地與月經週期有關，但這些情緒認知症狀背後之機轉，則尚未完全了解。本研究完成 97 名 PMDD 個案及 65 名控制組之研究與分析，針對經前不悅症之核心症狀如易怒症狀進行分析。逐月追蹤結果呈現敵意、憂鬱、焦慮、及衝動於月經週期顯著之變化。進一步探討行為反應模式，情緒控制型態，及注意力之表現，易呈現這些情緒之相關因素，於經前不悅症婦女亦呈現相同的月經起伏，其中情緒適應(affection adjustment)及注意力缺陷症狀於經前不悅症婦女呈現顯著之經前惡化傾向。進一步分析結果支持 freeze response to aversive stimuli, impaired affection adjustment, 及 inattentive behavior 與易怒相關，這些結果顯示，經前不悅症之核心症狀可能受到行為反應模式、情緒管理模式、及認知功能之影響。同時，也需要針對嫌惡刺激的反應模式，情緒控制型態及認知功能需要有深入的評估，以進一步了解經前不悅症之機轉。除此之外，本研究已發現 PMDD 患者於腦結構與功能性連結上之變異。其中，PMDD 婦女有較高之 cadate-insula connectivity，此可能顯示，PMDD 婦女之行為選擇，容易受到情緒生理反應之影響。進一步比較 functional connectivity 於經前與經後之影響，結果顯示 PMDD 婦女於經前 caudate 與 anterior cingulate 有較高之連結。除此之外，insula 間亦有較高之連結。這些研究結果顯示，經前不悅症婦女之功能性連結於經前有顯著的變異，顯示經前不悅症狀一系列情緒認知行為之症狀，可能與月經週期間之腦功能變異有關，值得進一步之研究。

中文關鍵詞：經前不悅症，敵意，情緒適應，注意力，灰質密度，功能性連結

英文摘要：Women with PMDD had a series mood, cognitive, and behavior symptoms in the premenstrual phase. The symptoms could be improved in follicular phase and exacerbated in the premenstrual phase. Since the underline neurobiological mechanism of PMDD had not been well understood, it is necessary to evaluate their neuro-behavior presentation among women with PMDD. A total of 97 women with PMDD and 65 controls had completed the first evaluation and complete the followed up study. The result demonstrated that women the PMDD had higher irritability, depression, anxiety, and impulsivity in both the premenstrual and

follicular phase. Further, the repeated measures evaluation reveal a premenstrual exacerbation in irritability, depression, anxiety, and impulsivity. We also demonstrated that women with PMDD had higher freeze response, lower affection adjustment, and higher inattentive symptoms. The further analysis demonstrated the premenstrual exacerbation in affection adjustment and inattentive behavior. Further, these two factors all contribute to not only irritability, but also depression. These result would suggest that emotion regulation style and cognitive function are essential in mechanism of PMDD symptoms, such as irritability and depression. Further, the women with PMDD had a higher GMD over occipital lobe than control. They also had a stronger caudate-insula connectivity than control group. The caudate-insula connectivity might indicate a behavior selection based somatic information. The higher connectivity might represent the vulnerability of behavior decision subject to somatic symptoms. Within PMDD group, their gray matter density over temporal and frontal lobe was higher in premenstrual phase those might indicate a higher blood flow. Lastly, they had a stronger caudate-anterior cingulate connectivity and insula connectivity in the premenstrual phase. This would indicate the inhibitory behavior and anxiety symptoms. Further analysis to reveal the clinical implication of the brain imaging study is necessary in future.

英文關鍵詞： PMDD, irritability, emotion regulation, attention, gray matter density, functional connectivity.

附件一

科技部補助專題研究計畫成果報告

（□期中進度報告/■期末報告）

經前不悅症之易怒機轉：情緒易感受性、情緒管理、與認知控制

計畫類別：■個別型計畫　□整合型計畫

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顏如佑　助理教授

龍震宇　副教授

計畫參與人員：學士級-專任助理人員：梁智媛

本計畫除繳交成果報告外，另含下列出國報告，共 _0_ 份：

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□出席國際學術會議心得報告

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3.「本報告」是否建議提供政府單位施政參考 ■否 □是，____（請列舉提供之單位；本部不經審議，依勾選逕予轉送）

中　華　民　國　102　年　10　月　27　日

附件二

科技部補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現（簡要敘述成果是否有嚴重損及公共利益之發現）或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■達成目標

□ 未達成目標（請說明，以 100 字為限）

□ 實驗失敗

□ 因故實驗中斷

□ 其他原因

說明：本研究為三年計畫之第一年計畫，第二年計畫因未獲補助，然本計畫仍完成前一年半之研究進度，完成 97 名 PMDD 個案及 65 名控制組之收集，並完成初步之問卷及訪談研究，並同時完成第二年之腦影像研究，進行結構化影像與功能性連結之初步分析。結果可呈現易怒症狀之相關因素，與廣泛性焦慮症之共病，及 PMDD 個案之腦結構及功能性連結變異，整體已達成預期之研究進度。

2. 研究成果在學術期刊發表或申請專利等情形：

論文：□已發表 □未發表之文稿 □撰寫中 ■無

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技轉：□已技轉 □洽談中 ■無

其他：（以 100 字為限）

研究結果充分，但因剛完成收案，資料整理中，尚未完成投稿。

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性），如已有嚴重損及公共利益之發現，請簡述可能損及之相關程度（以 500 字為限）

本研究完成 97 名 PMDD 個案及 65 名控制組之研究與分析，本研究針對易怒症狀進行分析，呈現其於月經週期顯著之變化，同時，進一步探討行為反應模式，情緒控制型態，及注意力於敵意上之角色。結果支持 freeze response to aversive stimuli, impaired affection adjustment, 及 inattentive behavior 與易怒相關，可作為進一步處理易怒症狀之依據。同時，也顯對嫌惡刺激的反應模式，情緒控制型態及認知功能需要有深入的評估，以進一步了解經前不悅症之機轉。除此之外，本研究已發現 PMDD 患者於腦結構與功能性連結上之變異。其中，PMDD 婦女有較高之 caudate-insula connectivity，此可能顯示，PMDD 婦女之行為選擇，容易受到情緒生理反應之影響。進一步比較 functional connectivity 於經前與經後之影響，結果顯示 PMDD 婦女於經前 caudate 與 anterior cingulate 有較高之連結。除此之外，insula 間亦有較高之連結。這些研究結果顯示，經前不悅症婦女之功能性連結於經前有顯著的變異，顯示經前不悅症狀一系列情緒認知行為之症狀，可能與月經週期間之腦功能變異有關，值得進一步之研究。

中文摘要

經前不悅症係指育齡之婦女在月經來潮之前一週，會出現顯著的情緒，認知，與行為上的變化。其症狀顯著地與月經週期有關，但這些情緒認知症狀背後之機轉，則尚未完全了解。本研究完成 97 名 PMDD 個案及 65 名控制組之研究與分析，針對經前不悅症之核心症狀如易怒症狀進行分析。逐月追蹤結果呈現敵意、憂鬱、焦慮、及衝動於月經週期顯著之變化。進一步探討行為反應模式，情緒控制型態，及注意力之表現，易呈現這些情緒之相關因素，於經前不悅症婦女亦呈現相同的月經起伏，其中情緒適應(affection adjustment)及注意力缺陷症狀於經前不悅症婦女呈現顯著之經前惡化傾向。進一步分析結果支持 freeze response to aversive stimuli, impaired affection adjustment, 及 inattentive behavior 與易怒相關，這些結果顯示，經前不悅症之核心症狀可能受到行為反應模式、情緒管理模式、及認知功能之影響。同時，也需要針對嫌惡刺激的反應模式，情緒控制型態及認知功能需要有深入的評估，以進一步了解經前不悅症之機轉。除此之外，本研究已發現 PMDD 患者於腦結構與功能性連結上之變異。其中，PMDD 婦女有較高之 caudate-insula connectivity，此可能顯示，PMDD 婦女之行為選擇，容易受到情緒生理反應之影響。進一步比較 functional connectivity 於經前與經後之影響，結果顯示 PMDD 婦女於經前 caudate 與 anterior cingulate 有較高之連結。除此之外，insula 間亦有較高之連結。這些研究結果顯示，經前不悅症婦女之功能性連結於經前有顯著的變異，顯示經前不悅症狀一系列情緒認知行為之症狀，可能與月經週期間之腦功能變異有關，值得進一步之研究。

關鍵詞： 經前不悅症，敵意，情緒適應，注意力，灰質密度，功能性連結。

Abstract

Women with PMDD had a series mood, cognitive, and behavior symptoms in the premenstrual phase. The symptoms could be improved in follicular phase and exacerbated in the premenstrual phase. Since the underline neurobiological mechanism of PMDD had not been well understood, it is necessary to evaluate their neuro-behavior presentation among women with PMDD. A total of 97 women with PMDD and 65 controls had completed the first evaluation and complete the followed up study. The result demonstrated that women the PMDD had higher irritability, depression, anxiety, and impulsivity in both the premenstrual and follicular phase. Further, the repeated measures evaluation reveal a premenstrual exacerbation in irritability, depression, anxiety, and impulsivity. We also demonstrated that women with PMDD had higher freeze response, lower affection adjustment, and higher inattentive symptoms. The further analysis demonstrated the premenstrual exacerbation in affection adjustment and inattentive behavior. Further, these two factors all contribute to not only irritability, but also depression. These result would suggest that emotion regulation style and cognitive function are essential in mechanism of PMDD symptoms, such as irritability and depression. Further, the women with PMDD had a higher GMD over occipital lobe than control. They also had a stronger caudate-insula connectivity than control group. The caudate-insula connectivity might indicate a behavior selection based somatic information. The higher connectivity might represent the vulnerability of behavior decision subject to somatic symptoms. Within PMDD group, their gray matter density over temporal and frontal lobe was higher in premenstrual phase those might indicate a higher blood flow. Lastly, they had a stronger caudate-anterior cingulate connectivity and insula connectivity in the premenstrual phase. This would indicate the inhibitory behavior and anxiety symptoms. Further analysis to reveal the clinical implication of the brain imaging study is necessary in future.

Key words: PMDD, irritability, emotion regulation, attention, gray matter density, functional connectivity.

目錄

壹、研究背景

經前不悅症係指育齡之婦女在月經來潮之前一週，會出現顯著的情緒變化，和明顯的生理轉變，使得婦女容易生氣憤怒，也感覺焦慮、憂鬱和不安，在生活品質上經常受到極大的影響，同時也因為這些不適症狀而重複就醫，增加了醫療支出，同時造成工作產能之下降，而造成非直接的經濟影響(Rapkin & Winer, 2009)。

曾有研究顯示 20-32% 的婦女至少有輕微之症狀(Biggs & Demuth, 2011)；Burt 則發現 5%的婦女符合 DSM-IV 經前不悅症之診斷準則(Burt VK & Hendrick VC 2001); 另一文獻回顧顯示 3-8% 生產年齡的女性達到經前不悅症之診斷準則(Biggs & Demuth, 2011)；在亞洲國家的發生率則約為 1.3%到 2.8%(Schatz, Hsiao, & Liu, 2012)。該疾病之症狀只發生在週產期，不會發生在停經後或未有月經之小孩(Burt & Stein, 2002)。過去研究結果顯示，經前不悅症於人群中佔相當比例，是女性停經前重要的，但亦被忽略的身心問題之一。

貳、研究目的

本研究假設經前不悅症婦女於經前之高負面情緒易感受性、認知控制資源受限、及情緒管理功能缺陷是導致易怒情緒的重要機轉 (假設圖一)。這些機轉可能與經前不悅症之長期機轉有關(如血清素缺陷)，而這些機轉於經前之惡化，則和血清素缺陷影響個體對女性荷爾蒙易感受性有關，而導致易怒於經前的惡化。兩者交互作用導致之認知資源缺陷亦進一步惡化情緒與認知控制，依據這樣的概念，，本研究之目的在整合功能性磁振造影(調查神經生物反應)、精神病理評估(客觀行為表現)、及問卷調查(主觀行為感受)之研究方式，以月經週期間追蹤研究模式，來觀察並驗證認知控制資源、情緒易感受性、與情緒管理缺陷於經前不悅症易怒情緒之角色與機轉。

參、文獻探討

一、 經前不悅症

（一）經前不悅症診斷準則

精神疾患診斷與統計手冊第 5 版草案(APA, 2012)經前不悅症之診斷準則為：

1.在過去一年多數月經週期裡，於黃體期最後一星期的多數時候，有下列症狀五項或五項以上，在濾泡期初發後幾天內即開始緩解，在月經後那星期即無症狀，1、2、3、及 4 的症狀中至少要有其一：

(1)顯著憂鬱心情、無望感受、或自我貶抑的想法。

(2)顯著焦慮、緊張感受、感覺被緊迫、或急躁。

(3)顯著情感易變(如突然感覺悲傷、或欲泣、或對拒絕增加敏感性)。

(4)持續而顯著生氣、或易怒、或增加人際衝突。

(5)平日活動(如工作、學校、朋友、嗜好)的興趣減少。

(6)主觀感受專注能力有困難。

(7)昏睡、易疲累、或顯著缺乏精力。

(8)胃口顯著改變、進食過多、或渴求特殊食物。

(9)嗜睡或失眠。

(10)主觀感受被壓制或將失去控制。

(11)其他身體症狀，諸如乳房壓痛或腫大、頭痛、關節或肌肉疼痛、膨脹(bloating)感覺、體重增加。

在經期婦女，黃體期指排卵到月經開始之間的時期；濾泡期指月經來時開始。在無月經婦女，如已子宮切除者，則需檢驗血液中生殖激素濃度，以判定黃體期及濾泡期的發生時刻。

2.此障礙顯著妨礙工作或學業、一般社會活動及與他人之關係(如畏避社會活動、在工作或學業的成就能力及效率變差)。.

3.此障礙不只是其他疾患的症狀惡化而已，如重鬱症、恐慌性疾患、低落性情感疾患、或一種人格疾患(但它可以與上述任何疾患共同發生)。

4.準則 A、B、C 必須在至少連續兩個有症狀的週期中，經事先規劃並逐日評量其症狀以證實(在此證實之前可先做暫時性診斷)。

二、經前不悅症之易怒(Irritability)

易怒是目前尚未被歸類為任何單一診斷的情緒症狀，截至目前僅有一篇文獻針對 irritability 提出文獻回顧(Stringaris, 2011)，但其著墨於其與精神疾病的關聯，而缺乏機轉之探討。在經前不悅症的症狀中，irritability 佔有非常重要之臨床重要性(Born, Koren, Lin, & Steiner, 2008)，其不僅造成情緒上的困擾，更影響人際關係。然而，不若憂鬱或焦慮有較清楚的機制，易怒的機轉目前了解仍十分有限。

Craig 將易怒定義為一種情緒(Mood)，是一個至少維持幾天到幾個禮拜的情緒狀態，使個案容易憤怒，產生敵意的認知，也容易出現攻擊的行為。不僅在主觀上感受到不愉快，在客觀上亦容易引起他人不悅，而造成人際上的問題(Craig, Hietanen, Markova, & Berrios, 2008)。所以易怒的評估必須涵蓋情緒、認知、及行為。過去有關易怒的評估工具中 irritability questionnaire 與 Buss-Durkee Hostility 為同時著墨情緒表現、認知內涵、及行為表現。除此之外，探討易怒之機轉也須要由情緒表現、認知解讀、及行為形成之過程加以討論。

情緒經由四個步驟產生，分別是環境中的刺激(stimuli in context)、注意到這個刺激(attention)、然後由經驗與認知來評估這個刺激的意義(appraisal)、再針對評估結果產生情緒反應(Ochsner, Silvers, & Buhle, 2012)。情緒產生後，個體會因為情緒而產生行為反應，例如在憤怒下出現攻擊的行為。在原始世界，外界的負面刺激被個體注意到，對此刺激產生敵意之解讀，而產生憤怒之情緒和必要的反擊行為。但現代社會複雜的人際互動使得憤怒的表現更為複雜，過度敵意之表現可能影響人際，所以經由認知控制來調控情緒，使生物體的情緒表現可以在競爭環境中取得優勢，是情緒管理的重要功能。所以個體可能經由這些調控機轉的運作，形成最後的情緒結果，再由前腦的決策機轉，來決定採取反應的行為。而易怒的情緒，則使得憤怒情緒容易產生，針對這樣的情緒，容易產生敵意的認知解讀，同時，最後容易產生攻擊或敵意的行為。

在這樣的過程中，並非所有個體都有相同的反應，對環境中情緒刺激的敏感性，如個體的生物特性(對壓力的敏感性)，可能決定個案是否產生原始的情緒反應，或是情緒反應的程度。心理與經驗特性(認知型態)，可能影響情緒產生後，對刺激的解讀，而影響敵意認知的產生。這時，依據環境中的需要，情緒管理能力將影響此個體是否能適當的轉化或調節情緒表現，來產生最有利之情緒反應。然而，當情緒形成，前腦須對行為做適當之決策，在很憤怒的情緒下，前腦決策型態將影響不利的攻擊行為的發生機會。

因此，如果要完整的觀察與了解易怒的機轉，除了須針對易怒的情緒、認知、及行為層面做調查，也須要針對易怒形成過程之相關因素進行調查，包括情緒的易感受性、情緒管理、認知控制、及最後的決策機轉。

三、易怒之相關因素

（一）情緒的易感受性

情緒反應的程度是過去情緒疾患十分重視的機轉之一，許多人格評估皆涵蓋過度反應的相關特質，最常見的如 neurotism 之人格特質對負面訊息過度敏感，而成癮相關疾患則對酬償訊息特別敏感。本研究著重於易怒之反應，對生活情境中的負面或威脅訊號會誘發生物個體產生原始的易怒反應，所以與易怒反應相關的情緒反應包括壓力(Kim & Haller, 2007)與嫌惡反應(Patrick, 2008)。對於這些反應之敏感度可能影響個體在遭遇這些負面刺激時的反應程度。

（二）敵意認知

敵意認知所指為對週遭刺激習慣以負面的認知方式進行解讀，對於他人的想法容易產生他人將對己不利或不公平的猜測，而顯示出對他人缺乏信任或充滿不安全感的認知模式(Ramirez & Andreu, 2006)。這樣的解讀模式在負面刺激下，容易產生敵意的反應和憤怒的情緒。

（三）情緒管理(emotion regulation)

當負面刺激誘發易怒情緒時，情緒是否能適當管理或控制，是個體維持適當情緒表現十分重要的功能。近十年來，情緒被認為是對個體有意義的事件所激發的神經生物反應，而情緒管理則被定義為一種有目的影響情緒經驗的面向、程度、與持續性，以維持情緒的

彈性在當下及長遠目標中達到平衡，而形成對個體有利之結果。在個體與環境的互動中，情緒訊息例如酬償或處罰，為優先被獲得的判斷資源之一(很快被感受到)。快速的評估並整合情緒訊息對原始動物存活如何產生有利的生存行為，扮演非常重要的角色。但相反的，不適當的運用、或全然依據情緒訊息來反應(未經認知思考)，也會導致精神疾患或生活功能缺損。近來發現，前腦在處理動作衝突 (反應抑制或選擇) 及情緒衝突(情緒呈現或自覺)上扮演重要的角色。除此之外，進行決策相關(決定我要做什麼)及情緒管理(我要如何感受)的腦區及運作模式，有相當的重疊(前腦)，顯示前腦同時扮演決策及情緒管理的角色，同時決策與情緒管理可能在運作上有著高度的關聯與整合，而 dorsomedial, dorsolateral, ventrolateral, and ventromedial regions of prefrontal cortex 可能在情緒管理及決策上扮演重要的角色(Mitchell, 2011)。

所謂情緒的管理即是改變上述的情緒產生過程，來控制或調整情緒的產生，以獲得對生物體生存有利之反應。而情緒的調整可能經由意識層面可以感知的 explicit emotion regulation 或是經由意識未能感知的(自動化的)implicit emotion regulation，來調整個體的情緒表現(Gyurak, Gross, & Etkin, 2011)。在 explict emotion regulation 中包含 situation modification 來避免或調整暴露刺激的機會或程度(如眼不見為淨)，或是 attention deployment 來減少對刺激的感受程度，包括 selective attention or distraction (顧左右而言它)來減少對刺激的反應。認知改變(cognitive change)是改變對事情的看法而影響對情緒的反應(如知足常樂或杞人憂天)，最重要的即是 reappraisal 之機轉，利用改變對事情的看法或意義而改變對事件的情緒反應，也是最常被運用在治療上的認知管理方式。而最後一種情緒管理是 repressive suppresion 經由抑制表情來影響情緒表現和感受(一笑泯千仇)。而執行這些控制，通常須要額外的認知資源，稱之為 effortful control(Cheetham, Allen, Yucel, & Lubman, 2010)。

（四）fMRI study for emotion regulation

情緒管理是一個經由神經系統的作用，表現在認知的訊息處理上，而呈現於生活中的行為與反應。所以，情緒管理的測量包括以問卷來了解個體的行為與認知模式，或以誘發電位理解可能的訊息處理，而功能性磁振造影，則是可以同時觀察行為與腦區活化，來提出可能的機轉。觀察的主要模式為被動的觀看正向或負面的情緒圖片，對圖片所產生的情緒反應和腦反應進行分析，來了解對正向或負面圖片之 emotion processing，之後在要求個案於 確不易確認所產生的情緒反應與假設相同，同時，亦與生活中之經驗不同(主要的情緒反應為與自身相關之事件)，另一類的觀察則是以測驗誘發正向或負向的情緒反應(如以 incentive delayed reward task 誘發 rewarding response 或是以賭博測驗誘發輸錢的反應)，並教導 reappraisal 之策略來抑制 rewarding or loss response 來觀察受試者 emotion regulation (reappraisal regulation) 之相關腦區(Sokol-Hessner, Camerer, & Phelps, 2012; Staudinger, Erk, & Walter, 2011)。除此，運用 social cognition 與 game theory 之理論，利用如 Ultimatum game，當遇到不平檔的選擇時，受試者須要抑制情緒反應來做選擇以最佳利益之反應，利用對這樣過程的觀察，可以了解這些互動中的情緒管理之腦功能狀態(Grecucci, Giorgetta, Van't Wout, Bonini, & Sanfey, 2012)。然而，雖然使用不同的方法，相關研究有相當一致的結果，amygdala 與 stimuli 之 arousal or threat value 有關，ventral striatum 則與 rewarding value 有關，anterior cingulate 扮演 conflict mentoring 的角色，dorsolateral prefrontal cortex 則與注意力選擇有關，ventral medial prefrontal cortex 則與刺激於當下環境的重要性或行為抑制有關，最後，insula 則與身體化的情緒線索有關。這些腦區在情緒管理過程扮演重要的角色(Ochsner et al., 2012)。

（五）認知控制與情緒控制

越來越多文獻顯示，情緒與認知兩者間有密切的影響，情緒能否控制得當，可能影響認知控制的能力(如負面情緒下控制能力變差)，而情緒控制與認知控制也使用共同的資源，兩者者為競爭資源或協同控制尚有爭議，但確認的是良好的認知控制，往往有助於情緒控制。過去研究即顯示，prefrontal lobe 與 anterior cingulate 這些於提供認知控制重要資源的腦活化，於情緒管理上扮演重要的角色。所以，認知資源是維持良好情緒管理

功能的基礎，然而，本研究團隊發現，經前不悅症患者於經前認知資源不論是注意力、反應抑制、認知功能均有顯著之缺陷。除此之外，經前的情緒症狀，亦可能惡化認知控制的能力，所以兩者之交互作用，可能是經前一系列情緒症狀之原因。也因此，本研究認為認知控制與情緒控制之交互作用(Pourtois, Notebaert, & Verguts, 2012)，是經前不悅症患者易怒情緒之重要機轉。

四、目前研究之不足與限制

易怒是經前不悅症婦女最重要的症狀之一，其不僅造成個案情緒上之痛苦，易怒和敵意的情緒更影響個案之人際關係。然而，和憂鬱或焦慮症狀不同，敵意並非單純的內在情緒問題，也合併外顯的行為問題。過去對於經前不悅症易怒之調查，多以症狀學的調查為主，同時缺乏多層面的評估，亦缺乏針對易怒的神經生物機轉之調查。有需要針對易怒進行完整之調查，以釐清其可能之機轉。

針對易怒可能之相關機轉如情緒易感受性、情緒管理、認知資源、認知控制過去少有完整相關之調查，近來陸續有研究提及認知資源與認知控制的缺陷，但與易怒的關聯尚未釐清。本研究團隊曾發現經前不悅症工作記憶缺陷與易怒有關(Yen et al., 2012)，但缺乏腦神經影像的觀察。故有必要針對這些重要因素進行整合性的調查，以瞭解經前不悅症婦女易怒之機轉。

女性荷爾蒙與壓力荷爾蒙皆與情緒表現有關，亦與經前不悅症機轉相關，但與經前不悅症婦女易怒症狀之關聯，則未有進一步之調查。

綜上所述，除了針對易怒應進行多層面的評估及腦影像之觀察(biological marker of irritability)，亦應針對可能之機轉，包括情緒易感受性、情緒管理、認知資源、認知控制進行完整及多層面的調查(包含腦影像檢查來了解相關機轉)。

肆、研究方法

一、研究個案

本研究以經前不悅症作為主要之研究標的，受試者為年滿 20 歲低於 35 歲之成人個案，具高中職以上學歷。

(一) 經前不悅症組(PMDD group)：

1. 研究組徵求條件為：符合精神疾患診斷與統計手冊第四版經前不悅症診斷標準之成年婦女。年齡介於 20-35 歲，具高中職以上學歷之個案。
   (1) 在月經週期來之前一週自覺心理與生理狀態與平時有明顯不同。
   (2) 在月經週期來之前一週於以下十一個症狀具有五項以上（含五項）：包括 1.情緒變得沮喪；2. 情緒容易緊張不安；3.情緒起伏大，例如容易突然傷心難過；4.容易生氣；5.對興趣或活動提不起勁；6.比平常更難集中精神；7.容易疲勞，體力變差；8.明顯的食慾變化，如變得愛吃甜食或其他食物；9.睡不著或睡太多；10.覺得被打敗或失控的感覺；11.身體不適（如頭痛、體重增加或水腫）。
   (3) 而且這些症狀在月經來後幾天內就明顯改善。
2. 受試者先經經前症狀篩檢量表（Premenstrual symptoms screening tool; PSST）篩選，符合中重度症狀表現個案進入診斷性會談。
3. 經精神科醫師依據精神疾患診斷與統計手冊第四版經前不悅症診斷標準進行診斷性會談，確診為經前不悅症個案。符合者收案為經前不悅症組。

(二) 對照組：為從未符合經前不悅症診斷之成年女性，依據年齡與學歷配對收案。

(1) 對照組徵求條件：
   (1) 在月經週期來之前一週自覺心理與生理狀態與平時並無顯著差異。
(2) 在月經週期來之前一週於上述 11 個症狀中具有 2 項以下，或超過兩項但十分輕微不會造成困擾：
(3) 受試者先經經前症狀篩檢量表（Premenstrual symptoms screening tool; PSST）篩選，未達中重度症狀表現個案進入診斷性會談。
(4) 經精神科醫師依據精神疾患診斷與統計手冊第四版經前不悅症診斷標準進行診斷性會談，未達經前不悅症診斷準則，同時，回顧過去病史，並無經前不悅症病史。符合者收案

為對照組。

(三) 本研究之排除條件: 1)懷孕或可能懷孕; 2)目前服用任何之 psychotropic medication、避孕藥、調經藥、減肥藥或非法藥物個案; 3)目前罹患可能導致身體危險之重大生理疾患; 4)合併智能障礙、精神病性疾患、自閉症、或器質性精神病等任何可能引起認知功能缺損而無法執行本研究相關測驗之個案。

二、研究工具

本研究之評估分為四大方向，包括功能性磁振造影、問卷與主觀評估、神經認知測驗、及生理評估：

（一）診斷性會談及工具

1.經前不悅症診斷問卷本（Diagnostic schedule of Premenstrual Dysphoric disorder based on DSM-IV-TR）：依據 DSM-IV-TR PMDD research criteria 發展之半結構化問句，以作為診斷經前不悅症之依據。

2.中文版簡短神經精神診斷會談手冊-台灣 MINI(The Chinese version of the Mini-International Neuropsychiatric Interview (MINI)): MINI 為 Sheehan 依據 DSM-IV 所發展之結構化診斷工具(Sheehan et al., 1998)，本研究以台灣 MINI 作為診斷受訪者目前有無重鬱症、輕鬱症、社交恐懼症、廣泛性焦慮疾患及強迫症。並作為排除物質依賴或濫用之診斷依據。在與 SCID-P 的對照研究中，MINI 具有好到很好的 kappa value，同時具有高於 70%之敏感度，85%之特異性，以及 75%之診斷正確性。結果顯示，MINI 在診斷上有極佳之效度。

（二）功能性磁振造影

本研究以功能性磁振造影調查經前不悅症之腦活化缺陷，以本院之 GE 3T MR systems 作為影像收集工具。

1.結構化影像

以 3D FSPGR (fast spoiled gradient echo) magnetic resonance imaging 之方式收集結構影像以分析 voxel based morphology，來分受試者在腦部結構上有無顯著差異。收集之影像條件為 a sagittal three-dimensional gradient-echo T1-weighted sequence (repetition time: 9 msec; echo time: 3.5 msec; matrix 256 × 256; voxel size: 1 × 1 × 1 mm; 170 slices)。

2.功能性影像

以 EPI 作為收集功能性磁振造影影像之工具。gradient-recalled echo planar imaging (EPI) sequence (64X64 matrix; 24 cm field of view, echo time [TE]= 35 milliseconds; repetition time [TR]=2 seconds; 3-mm thick slices with 0-mm gap)

3.靜止功能影像

以 10 分鐘之時間，收集靜止 EPI 之訊號，以作為分析受試者之 functional connection 之差異。本研究將採取 Seed-voxel correlation 之分析方式，依據過去之研究結果，將以 anterior cingulate, posterior cingulate, insula 做為 Seed 來做進一步分析。同時亦進行 regional homogeneity 與 amplitude of low frequency fluctuation 之評估。

4.參與功能性磁振造影受試者之排除條件

(1)嚴重之身體疾患包括急性氣喘發作、心肌梗塞、或腦血管疾病

(2)任何之金屬植入物

(3)功能性磁振造影之 contraindication：如狹窄空間恐懼、大片刺青等

(4)目前服用可能影響腦功能之中樞神經藥物

（三）行為量表包含

1.有關經前不悅症之調查

(1)經前症狀篩檢量表(Premenstrual symptoms screening tool; PSST)

本量表由 Steiner 所發展，為適合臨床人員使用之篩檢工具，本工具由受訪者自行填寫，同時依據 DSM-IV-TR 之精神作最後診斷(Steiner, Macdougall, & Brown, 2003)，本量表可作為篩檢經前不悅症之工具。

(2)經前症狀週評估追蹤簡易問卷

由本團隊依據 DSM-IV-TR 所發展，針對 11 項症狀，以 1 到 4 分評估嚴重程度，作

為每週追蹤之工具，其內部一致性為 0.97，兩週再測信度為 0.87。於本研究用以追蹤 2 個月的時間，以確認診斷。

2.有關核心情緒症狀之調查

(1)簡氏中文敵意量表

本量表共計 20 題，分別評估敵意的四個面向，包括敵意認知、敵意情緒、外顯敵意行為、及敵意壓抑。其由 44 題版之中文敵意量表(Lin & Weng, 2002)發展而來。初步研究顯示其具有良好之內在一致性(0.93)及兩週再測信度為 0.80。

(2)The irritabiilty questionaire

此問卷針對易怒的情緒、認知、及行為做評估，並同時測量其頻率與程度，是一個完整觀察易怒之自填問卷。本研究以此做為易怒之評估。(Craig et al., 2008)

(3)中文版 CES-D 憂鬱量表

由鄭等人發展(Chien & Cheng, 1985)，用以評估過去一個禮拜中憂鬱症狀的頻率，分數由 0(沒有或很少)到 3(幾乎每天)，分數越高代表憂鬱程度越高。(Yang, Soong, Kuo, Chang, & Chen, 2004)。

(4) Penn state worry questionnaire (PSWQ)

用來評估焦慮程度，為五分 Likert's sclae，共計 16 題，其中五題為反向題，其具有良好之信效度，經常用來作為評估 general anxiety disorder 之工具。

3.與情緒處理及因應有關之量表

Affective Style Questionnaire 測量慣用之情緒管理模式(Hofmann & Kashdan, 2010)包含 concealing (消除)，adjustment (因應)，tolerance (忍耐)。

4.測量情緒易感受性有關之量表

以 Jackson-5 scales 代表對酬償與嫌惡之反應程度(Carver & White, 1994); (Jackson, 2009); 其重點著重於對嫌惡之反應，包括 behavior inhibition, flighting, flighting, and freeze response.

5.以 Barratt Impulsiveness Scale (BIS11)調查衝動(Patton, Stanford, & Barratt, 1995)

由 BIS 10 修改而來，用以測量衝動控制，經因素分析可區分 Attentional Impulsiveness, Motor Impulsiveness, and Nonplanning Impulsiveness 三個因子。同時具有良好之內在信度 0.79-0.83，為一個廣泛使用於衝動測量之量表。本研究使用為李等人所翻譯之中文版 BIS-11 量表。

(四) 生化及荷爾蒙指標:包括與情緒管理有關之基因 (此部分因經費不足，未能執行，將保留檢體，待經費充分下進行)

(1) Serotonin 有關之基因多型性:如 5-HTTLPR, HTR1A, MAOA 等。

(2) 與經前不悅症有關之基因：estrogen receptor alpha gene(Huo et al., 2007) , BDNF 等。

(3) 與壓力因應有關之荷爾蒙如 Corticotrophin releasing factor, ACTH; 與 emotion regulation 有關之荷爾蒙如 Oxytocin, vesopressin；或與衝動有關的 Ghrelin 等。

(4) 月經相關荷爾蒙：如 estrogen, progesteron, LH, FSH 等。

(5) BMI 、體脂肪等調查。

三、研究進行方式

(一) 先由研究助理於電話中確認條件，並排除懷孕、目前正服用任何 psychotropic medication、避孕藥、調經藥、減肥藥或非法藥物，並完成初步說明後，邀請參加研究，於完成同意書後將同意受試之成年女性分為研究組(以下稱 PMDD 組)與對照組，預計徵求 PMDD 組與對照組各 150 名。

(二) 再針對 PMDD 組與對照組個案由精神科醫師進行診斷性會談，依據 DSM-VI-TR research criteria(診斷問卷本)之要求，進行最後之診斷確認。

(三) 依據受訪者之最後一次月經週期分別安排於黃體期與濾泡末期(接近排卵期)各進行一次測驗(問卷、及生理評估)，為避免 order effect，PMDD 組與對照組各有一半之受訪者先在黃體期接受第一次評估，另一半會在濾泡期接受第一次評估，第一次評估時同時進行基因多型性之抽血檢查。

(四) 診斷性會談：於第一次評估，由精神科醫師進行診斷性會談，依據 DSM-IV-TR PMDD

research criteria 診斷經前不悅症，依據 MINI-CEX 診斷社交恐懼症，廣泛性焦慮疾患，及強迫症。

(五) 黃體期評估：1)問卷評估：所有問卷評估，包含 PMDD 症狀之檢核(self reported questionnaire)，及共病精神症狀之症狀檢核問卷;進行生理因子評估(女性荷爾蒙、及壓力荷爾蒙等評估)

(六) 濾泡末期評估：1)問卷評估：所有問卷評估，包含 PMDD 症狀之檢核(self reported questionnaire)，及共病精神症狀之症狀檢核問卷;進行生理因子評估(女性荷爾蒙、及壓力荷爾蒙評估)。

(七) 完成第一次評估後，每位受訪者每週均會收到一封電子郵件，提醒受訪者完成「經前症狀週評估追蹤簡易問卷」，追蹤 2 個月的時間，以確認診斷。

完成上述研究後，於 PMDD 組與對照組依據 fMRI 受試者之條件，各篩選經前不悅症個案及對照組各 30 人，於經前及經後完成抽血之生理檢驗後，各進行一次功能性磁振造影掃描。

伍、結果與討論

一. A total of 97 women with PMDD and 65 controls had complete the first evaluation and complete the followed up study. They were recruited in the final analysis.

二. The irritability, depression, anxiety, and impulsivity of Women with PMDD:

1. Women with PMDD had higher score in irritability, depression, anxiety, impulsivity than the control group not only in premenstrual phase, but also in follicular phase. This would suggest that they had a higher mood and impulsivity symptoms even in the base line. (table 1)

2. The repeated measure two factors ANOVA demonstrated that the PMDD effect was interacted with menstrual cycle effect on irritability, depression, anxiety, and impulsivity. These result will suggest that women of PMDD exacerbated their irritability, depression, anxiety, and impulsivity in comparison to control group.

3. These result would suggest women with PMDD had a higher base line symptoms. The symptoms exacerbated in the premenstrual phase. Thus, aside of factors contribute to menstrual cycles, the factors contribute to PMDD vulnerability could also contribute to these symptoms.

Table 1. The difference in irritability, depression, anxiety, and impulsivity between women with PMDD and controls.

	PMDD Case(N=97)		Control(N=65)		
Variables	Mean	SD	Mean	SD	F
P Irritability	60.02	12.38	49.95	11.44	-5.229***
F Irritability	56.71	11.35	50.00	11.77	-3.635***
P Depression	23.08	8.69	9.09	5.61	-12.449***
F Depression	18.61	10.26	8.15	5.20	-8.531***
P Anxiety	53.68	9.70	45.97	8.62	-5.182***
F Anxiety	50.88	9.54	46.51	9.09	-2.911**
P Impulsivity	72.65	9.30	67.32	7.76	-3.812***
F Impulsivity	70.96	8.36	68.25	8.08	-2.051*

P: premenstrual; F: follicular

Table 2. The interaction of PMDD and menstrual cycle effect on irritability, depression, anxiety, and irritability.

		Within-subjects					Between-subjects		
		df	Mean square	F			df	Mean square	F
Irritability	MC	1	207.21	5.813*	Irritable	Intercept	1	913694.49	3786.849***
	MC* PMDD	1	219.10	6.146*		PMDD	1	5478.05	22.704***
Depression	MC	1	570.12	12.079**	Depressive	Intercept	1	67594.96	797.911***
	MC* PMDD	1	243.28	5.154*		PMDD	1	11627.99	137.260***
Anxiety	MC	1	99.89	4.935*	Anxious	Intercept	1	755476.17	4918.249***
	MC* PMDD	1	217.42	10.741**		PMDD	1	2839.61	18.486***
Impulsivity	MC	1	11.47	0.908	Impulsive	Intercept	1	1516704.03	11537.970***
	MC* PMDD	1	132.95	10.532**		PMDD	1	1257.61	9.567**

三、The mood associated factors of women with PMDD

1. We firstly evaluate the response to reward and aversive stimuli with Jackson's 5 scale. Women with PMDD had lower behavior inhibition (a defensive approach) in premenstrual phase and had higher freeze response in both premenstrual and follicular phase. However, the repeated measure ANOVA demonstrated that they decline their behavior activation in premenstrual phase. This would indicate their baseline freeze response are higher than controls. Further, they decrease their behavior activation in premenstrual phase.

2. We then evaluate their affective style. It demonstrated that women with PMDD had lower ability to adjust or tolerate their affection in the premenstrual phase. This would indicate they had impaired their mood regulation in the premenstrual phase through impaired adjustment and tolerance of affection. The repeated measures two factors ANOVA demonstrated that the menstrual effect interacted with PMDD effect on adjustment of affection. This would suggest that women with PMDD further impaired their mood regulation with adjustment in the premenstrual phase.

3. The questionnaire demonstrated the inattention in the premenstrual phase. The questionnaire demonstrated that women with PMDD had higher inattentive behavior not only in the premenstrual phase, but also in the follicular phase. Although the inattentive behavior exacerbated in the premenstrual phase, this result might indicate the attentional resource is impaired among women with PMDD across the menstrual cycle.

Table 3.

	PMDD Case (N=97)		Control (N=65)		
Variables	Mean	SD	Mean	SD	T
P Behavior activation	22.20	3.69	22. 88	3.53	1.173
F Behavior activation	23.47	3.01	22.28	4.12	-2.136*
P Behavior inhibition	22.06	3.57	23.26	3.14	2.196*
F Behavior inhibition	22.55	3.51	22.73	3.48	0.334
P Fight	15.45	4.26	14.52	3.52	-1.459
F Fight	15.19	4.00	14.25	4.02	-1.463
P Flight	20.85	3.69	20.11	4.10	-1.192
F Flight	20.94	3.72	19.31	4.08	-2.629**
P Freeze	18.84	3.18	17.63	3.19	-2.359*
F Freeze	18.47	3.51	17.35	3.41	-2.014*
P Concealing	26.30	5.27	26.83	5.78	0.605
F Concealing	26.72	6.01	27.25	5.01	0.581
P Adjustment	23.41	3.73	25.91	3.98	4.066***
F Adjustment	24.42	3.82	25.80	3.86	2.240*
P Tolerance	16.96	2.73	17.83	2.44	2.078*
F Tolerance	17.40	2.58	17.97	2.49	1.390
P Attentional deficit	27.35	9.23	14.78	8.66	-8.701***
F Attentional deficit	23.68	10.65	15.47	8.40	-5.183***

P: premenstrual; F: follicular

Table 4.

		Within-subjects					Between-subjects		
		df	Mean square	F			df	Mean square	F
BAS	MC	1	8.68	1.759	BAS	Intercept	1	157741.88	7897.071***
	MC* PMDD	1	68.63	13.932***		PMDD	1	12.19	0.610
Flight	MC	1	12.19	2.312	Flight	Intercept	1	126246.75	5124.155***
	MC* PMDD	1	18.61	3.528		PMDD	1	102.21	4.149*
Freeze	MC	1	8.94	2.758	Freeze	Intercept	1	100702.62	4304.680***
	MC* PMDD	1	0.01	0.004		PMDD	1	93.19	4.909*
Adjustment	MC	1	18.41	4.397*	Adjustment	Intercept	1	190164.41	7473.959***
	MC* PMDD	1	20.83	4.976*		PMDD		294.53	11.576**

Tolerance	MC	1	6.30	2.282	Tolerance	Intercept	1	94332.17	8814.90***
	MC* PMDD	1	2.00	0.725		PMDD	1	37.97	3.548
Attention	MC	1	180.08	4.786*	Attention	Intercept	1	127075.21	910.003***
	MC* PMDD	1	399.68	10.623**		PMDD	1	8450.41	60.515***

四、The correlates of irritability in premenstrual phase among women with PMDD: To understand the factors contributing to irritability, we evaluate the association between irritability and others factors in premenstrual phase among women with PMDD. It demonstrated a close association between core symptoms of PMDD. Further, PMDD women with higher irritability had higher freeze and attentional deficit and lower affection adjustment. This would suggestion that cognitive function, emotional regulation, and response to aversive stimuli all contribute to the irritability of PMDD women.

Table 5.

	Irritability	Depression	Anxiety	Impulsivity	BIS	Flight	Freeze	Adjustment	Tolerance
Irritability	1								
Depression	0.381***	1							
Anxiety	0.426***	0.384***	1						
Impulsivity	0.229*	0.174	0.102	1					
BAS	-0.034	-0.131	-0.015	0.112	1				
Flight	0.129	-0.034	0.239*	0.029	0.222*	1			
Freeze	0.237*	0.316**	0.308**	0.150	-0.138	0.258*	1		
Adjustment	-0.430***	-0.297**	-0.443***	-0.135	0.165	-0.185	-0.199	1	
Tolerance	-0.116	-0.203*	-0.323**	0.091	0.088	-0.113	-0.108	0.547***	1
Attentional deficit	0.358***	0.413***	0.183	0.526***	-0.051	0.086	0.176	-0.237*	-0.059

五、The comorbidity of PMDD and role of irritability

1. Our result demonstrated that women with PMDD were more likely to have general anxiety disorder. Further, women with IGD had higher irritability, freeze response, lower affection adjustment and higher attentional deficit. These results are compatible to criteria of GAD.

2. The regression model demonstrate that GAD was significant associated with PMDD. Further, under control of irritability, the association between insignificant. It would suggest that irritability could be a significant mediating factor to the association between PMDD and GAD.

3. This result suggest that irritability palyed an important role in the comorbidity of PMDD.

Table 6. The association between PMDD and general anxiety disorder.

	PMDD Case (N=97)		Control (N=65)		Chi-squared
Variables	N	%	N	%	test
Generalized anxiety disorder	15	15.5	2	3.1	6.358*

Table 7. The association between GAD and irritability, behavior inhibition, flight, freeze, adjustment, tolerance, attentional deficit.

	Generalized anxiety disorder (N=18)		Normal (N=187)		
Variables	Mean	SD	Mean	SD	T
Irritability	63.11	10.20	54.95	12.79	-2.626**
BAS	22.78	3.61	22.58	3.55	-0.228
Flight	20.67	3.25	20.41	3.91	-0.273
Freeze	20.06	3.56	17.83	3.48	-2.591*
Adjustment	21.89	3.72	24.90	4.01	3.056**
Tolerance	16.17	2.41	17.43	2.62	1.963
Attentional deficit	28.39	9.29	21.57	10.89	-2.566*

Table 8. The regression model for PMDD.

	β	S.E.	Wald	OR	95% C.I.
Model I					
GAD	1.75	0.77	5.157*	5.76	1.27-26.12
Model II					
GAD	1.35	0.79	2.92	3.87	0.82-18.27
Irritability	0.07	0.02	17.89***	1.07	1.04-1.10

六、The evaluation for gray matter density of PMDD table 9, 10

1.The voxel based morphometric analysis demonstrated women with PMDD had higher gray matter density over occipital lobe. However, the difference is just over significance threshold.

2.The analysis also demonstrate women of PMDD had higher gray matter density over temporal and frontal lobe in premenstrual phase than those in follicular phase. As this is a paired t test, the difference should be further evaluated. Although they could be insignificant under FDR correction, the difference might indicate the blood flow change in different phase of menstrual cycle. Figure

Table 9. Brain areas with higher gray matter density among women with PMDD than those among controls

Region of activation			Talairach coordinates						
	R[c] /L[d]	BA[e]	X	Y	Z	Voxels	Z[f]	P	P[G]
Control									
Cerebulum	R	0/0	53	-55	-48	224	4.02	<0.001	0.025
Occipital_Inf	L	19/19	-30	-81	-3	3.82	191	<0.001	0.037
Lingual	R	18/18	18	-100	-8	3.39	323	<0.001	0.009
Fusiform	R	37/37	39	-57	-11	3.29		<0.001	

[G] *P:* p value in cluster level.

Table 10. The brain areas with higher gray matter density in premenstrual phase than those in follicular phase among women with PMDD.

Region of activation			Talairach coordinates						
	R[c] /L[d]	BA[e]	X	Y	Z	Voxels	Z[f]	P	P[G]
PMDD Luteal									
Temporal_Pole_Mid	L	38/38	-54	14	-27	763	4.13	<0.001	0.000
Frontal_Mid	R	46/46	31	45	24	153	4.06	<0.001	0.013
Frontal_Mid	R	46/46	40	45	30		3.42	<0.001	
Precentral	R	6/6	37	3	52	108	3.75	<0.001	0.033
Frontal_Inf_Orb	R	0/0	54	36	-9	108	3.63	<0.001	0.033
Precentral	L	6/6	-54	2	40	201	3.61	<0.001	0.006
Precentral	L	6/6	-53	-1	48		3.23	0.001	

[G] *P:* p value in cluster level.

七、The differences in functional connectivity between PMDD and control group in premenstrual phase.

1.The functional connectivity analysis demonstrated that women with PMDD had higher functional connectivity between ipsilateral nucleus caudate and insula than those in control group.

2.As caudate paly an important role in emotional processing, a stronger caudate and insula might indicate the somatic feeling from insula was strong connect to caudate. It might explain why women with PMDD had stronger emotional expression under menstrual cycle.

Table 11.

Region of Seed			MNI coordinates						
	R[c] /L[d]	BA[e]	X	Y	Z	Voxels	Z [f]	P	P[G]
Left caudate									
Temporal_Sup	R	22/22	63	-12	12	344	3.30	0.012	<0.001
Insula	R	48/48	45	-3	-3		3.24		0.001
Postcentral	R	43/43	66	-12	27		3.21		0.001
Right caudate									
Insula	L	48/48	-42	-9	0	353	3.45	0.010	0.001
Frontal_Inf_Orb	L	47/47	-33	24	-9		3.43		0.001
Insula	L	48/18	-36	15	-12		3.26		0.001

[G] *P:* p value in cluster level.

八、The differences in functional connectivity of PMDD women between premenstrual phase and follicular phase.

1.The result demonstrated that women with PMDD had higher functional connectivity to left caudate over anterior cingulate. The same presentation was noted to right side. These indicate they had a higher caudate-anterior cingulate connection in the premenstrual phase than those in follicular phase.

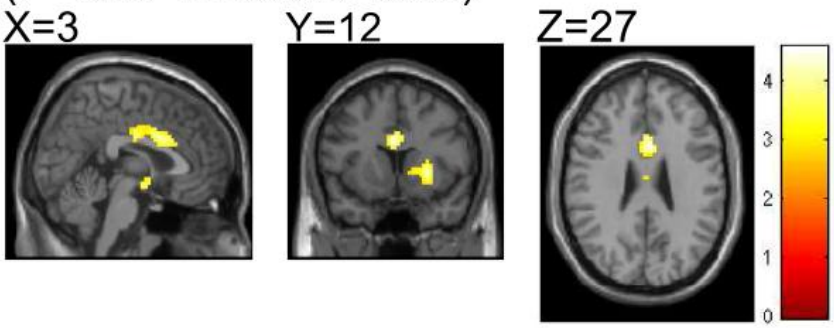
2.Further, they also had a stronger bilateral insula connection in the premenstrual phase than those in follicular phase.

Table 12. The brain areas with functional connectivity higher in premenstrual phase than those in follicular phase among women with PMDD

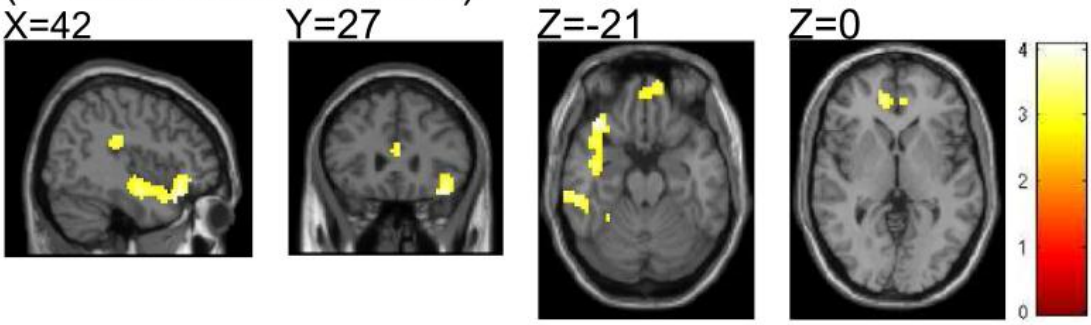
			MNI						
	R[c] /L[d]	BA[e]	X	Y	Z	Voxels	Z [f]	P	P[G]
Left Caudate									
Temporal_Pole_Sup	R	38/38	45	12	-24		3.10	0.013	0.001
Frontal_Mid_Orb	R	10/10	12	45	0	210	3.25	0.034	0.001
Cingulum_Ant	R	0/0	3	6	30		3.24		0.001
Right Caudate									
Cingulum_Ant	R	24/24	3	9	30	279	3.74	0.014	<0.001
Cingulum_Mid	R	24/24	9	0	39		3.32		<0.001
Temporal_Pole_Sup	R	38/38	45	12	-24		3.16		0.001
Rolandic_Oper	R	48/48	45	-30	24	180	3.19	0.041	0.001
Heschl	R	48/48	36	-24	18		3.17		0.001
Right insula									
Temporal_Sup	R	0/0	48	3	-9		Inf.		<0.001
Insula	L	48/48	-33	15	6	913	6.52	<0.001	<0.001

Temporal_Pole_Sup	L	38/38	-54	12	-9	6.05	<0.001
Temporal_Sup	L	38/38	-60	6	-3	4.77	<0.001

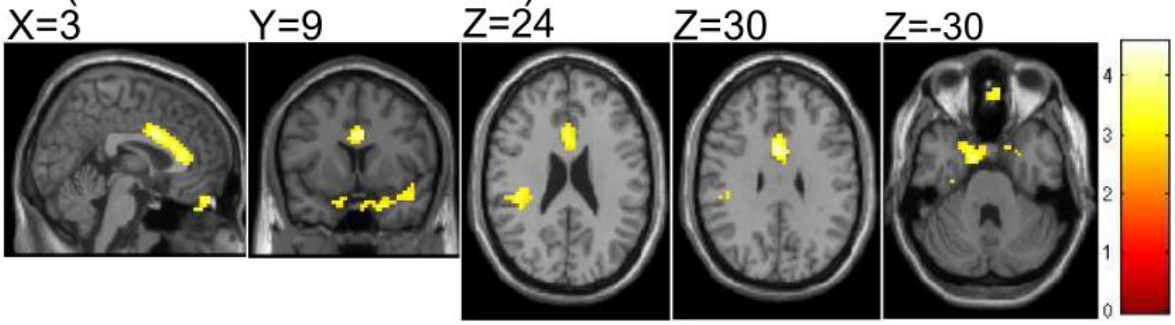
A.The brain areas with higher functional connectivity to right amygdala in premenstrual phase than those in follicular phase among PMDD group.
(P<0.05 in cluster level)



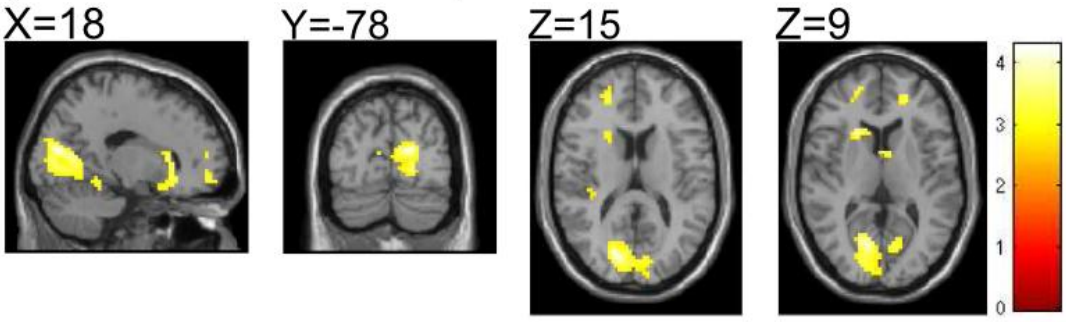
B.The brain areas with higher functional connectivity to left caudate in premenstrual phase than those in follicular phase among PMDD group.
(P<0.05 in cluster level)



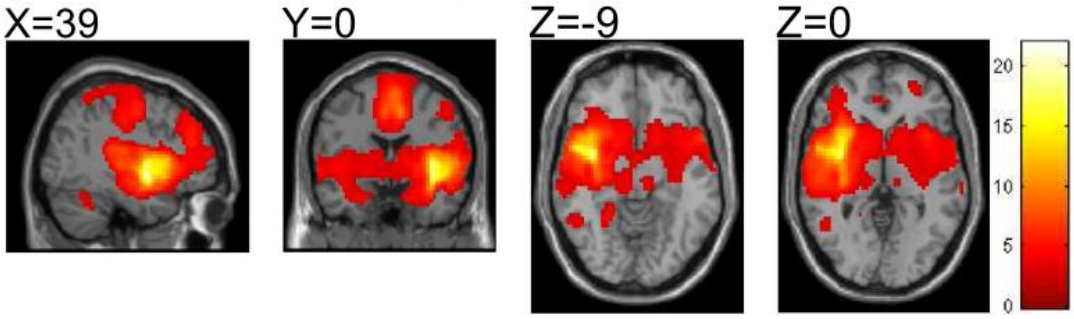
C.The brain areas with higher functional connectivity to right caudate in premenstrual phase than those in follicular phase among PMDD group.
(P<0.05 in cluster level)



D.The brain areas with higher functional connectivity to left anterior cingulate in premenstrual phase than those in follicular phase among PMDD group.
(P<0.05 in cluster level)



E.The brain areas with higher functional connectivity to right insula in premenstrual phase than those in follicular phase among PMDD group.
(P<0.05 in cluster level)



陸、結論與建議

The study demonstrate that women with PMDD had higher irritability not only in the premenstrual phase, but also in the follicular phase. Further, the irritability increased significantly in the premenstrual phase. This result supported that irritability demonstrated a menstrual cycle change as previous definition of PMDD. Further, other core symptoms, such as depression, anxiety, and impulsivity have the same presentation. However, the premenstrual exacerbation was stronger in anxiety and impulsivity. This result indicated that anxiety is another important symptoms of PMDD.

We further evaluated the associated factors of emotional regulation. The evaluation for reward and aversion sensitivity demonstrated that women with PMDD had a lower defensive approach behavior (BIS) in the premenstrual phase. Further, they are more likely to take freeze response when meeting aversive response not only in premenstrual phase, but also in follicular phase. This is compatible to their clinical symptoms, lack of interest and motivation, in the premenstrual phase. However, as the freeze was also significant higher in follicular phase. It might represent some characteristic contributing to PMDD symptoms. The further analysis revealed a significant association between freeze response and irritability in premenstrual phase among women with PMDD. The association might indicate the irritability might represented as anger in behavior. It is compatible to our clinical experience. Most subjects with PMDD feel anger, but try to suppressed in the premenstrual phase. However, this would contribute their cardiovascular risk.

Then, we evaluated the affective style of PMDD. The result demonstrated that they had lower affection adjustment and tolerance in the premenstrual phase. They might explain why they had higher irritability, depression, and anxiety symptoms in the premenstrual phase. The further evaluation demonstrated that affection adjustment was deteriorated in the premenstrual phase. This would suggest the impaired affection adjustment could be the characteristic of emotion regulation of PMDD. The correlation analysis demonstrated that affection adjustments negatively associated with depression, anxiety, and irritability in premenstrual phase among women with PMDD. This result would support that impaired affection adjustment contributed to irritability of PMDD.

Our data also demonstrated that women with PMDD had poor attention both in premenstrual and follicular phase. This would indicated that they had an impaired attention in the base line. The repeated measures analysis support that the attention deteriorated in the premenstrual phase. Further, PMDD women with higher inattentive symptoms had higher depression and irritability in the premenstrual phase. This would support that cognitive function play an important role in emotion regulation in the premenstrual phase. As the cognitive effort was necessary to control the emotion, PMDD women with impaired cognitive resource will had a difficulty in regulate their mood. Thus, it is important to enhance their cognitive function or cognitive resource to assist the women with PMDD.

We also evaluated the association between PMDD and general anxiety disorder. The result demonstrated that women with PMDD are more likely to had general anxiety disorder. The further evaluation demonstrated that irritability mediate the association between PMDD and GAD. This suggest irritability play an important role in the PMDD and GAD.

We then evaluated the change in brain structure change among women with PMDD. The between group analysis demonstrated that women with PMDD had higher gray matter density over occipital lobe. However, the difference is just over significance threshold. As the occipital lobe had the most important role in visual system. However, it is not the core symptoms of PMDD. Thus, its clinical significance deserved further evaluation. On the other hand, women of PMDD had higher gray matter density over temporal and frontal lobe in premenstrual phase than those in follicular phase. However, it is not reasonable that the brain structure would change in two weeks. As the BOLD signal is vulnerable to blood flow, the reached threshold difference might indicate the menstrual-phase dependent blood flow over temporal and frontal lobe. A further correlation analysis was necessary to reveal the clinical interpretation of these brain structure change.

The most important evaluation is the resting-functional connectivity study. Our result demonstrated that that women with PMDD had higher functional connectivity between ipsilateral nucleus caudate and insula than those in control group. Previous reviews conclude that the caudate nucleus contributes to behaviour through the excitation of correct action schemas and the selection of appropriate sub-goals based on an evaluation of action-outcomes; both processes fundamental to successful goal-directed action. This is in contrast to the putamen, which appears to subserve cognitive functions more limited to stimulus-response, or habit, learning. This modular conception of the striatum is consistent with hierarchical models of cortico-striatal function through which adaptive behaviour towards significant goals can be identified (motivation; ventral striatum), planned (cognition; caudate) and implemented (sensorimotor coordination; putamen) effectively(Grahn, Parkinson, & Owen, 2008).

The caudate-insula connectivitvy had been suggest to play a role in reward process and contribute to obesity(Nummenmaa et al., 2012). Thus, the higher connectivity between caudate and insula might represent another symptoms of PMDD, over eating in the premenstrual phase. Further, the high connectivity between caudate and insula might also indicate they select their behavior highly based on somatic information. In the premenstrual phase, this would make them make impulsive behavior based on their somatic discomfortable. However, the claim should be proved in future study. Or further correlation analysis was necessary.

Further analysis for functional connectivity between premenstrual phase and follicular phase also demonstrated the connectivity difference over caudate and insula among women with PMDD. It demonstrated that women with PMDD had a stronger connectivity between caudate and anterior cingulate in the premenstrual phase. Since anterior cingulate is essential in error processing and inhibition, this would indicated that their behavior was highly inhibited in premenstrual phase. This result is compatible to this presenting result showing highly freeze among women in PMDD.

On the other hand, we also demonstrated a stronger connectivity over insula among women with PMDD. The stronger insula association might indicate the higher somatic symptoms and the concern to somatic symptoms in the premenstrual phase. As insula participating the network essential for emotional process, the higher connectivity over insula had been suggest to indicate a symptoms of anxiety. This would compatible to our result that PMDD women had higher anxiety symptoms.

Our result demonstrate a significant premenstrual exacerbation in depression, irritability, anxiety, and impulsivity among women with PMDD. The freeze response, affection adjustment, and inattentive symptoms might contribute to irritability of PMDD in the premenstrual phase. The PMDD was significant associated with GAD and irritability mediate the association. The women with PMDD had a higher GMD over occipital lobe than control. Further, they had a stronger caudate-insula connectivity than control group. Within PMDD group, their gray matter density over temporal and frontal lobe was higher in premenstrual phase those might indicate a higher blood flow. Lastly, they had a stronger caudate-anterior cingulate connectivity and insula connectivity in the premenstrual phase. This would indicate the inhibitory behavior and anxiety symptoms. Further analysis to reveal the clinical implication of the brain imaging study is necessary in future.

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科技部補助計畫衍生研發成果推廣資料表

日期:2014/09/02

科技部補助計畫	計畫名稱: 經前不悅症之易怒機轉：情緒易感受性、情緒管理、與認知控制(重點代號: GM08)
	計畫主持人: 柯志鴻
	計畫編號: 102-2629-B-037-001- 學門領域: 性別主流科技計畫

無研發成果推廣資料

102 年度專題研究計畫研究成果彙整表

計畫主持人：柯志鴻	計畫編號：102-2629-B-037-001-
計畫名稱：經前不悅症之易怒機轉：情緒易感受性、情緒管理、與認知控制(重點代號:GM08)	

成果項目			量化			單位	備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等）
			實際已達成數（被接受或已發表）	預期總達成數(含實際已達成數)	本計畫實際貢獻百分比		
國內	論文著作	期刊論文	0	0	100%	篇	
		研究報告/技術報告	1	0	100%		國科會報告
		研討會論文	1	0	100%		精神醫學會報告
		專書	0	0	100%		
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（本國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	1	0	100%		1
國外	論文著作	期刊論文	0	3	100%	篇	本研究目前有數個明確之結果，一經前不悅正敵意受到情緒適應能力與注意力缺陷之影響，此兩因素亦隨月經週期起伏，二 經前不悅正與廣泛性焦慮症之共病因素，三經前不悅症於caudate and insula之腦估能性連結變異。
		研究報告/技術報告	0	0	100%		國科會報告
		研討會論文	1	0	100%		
		專書	0	0	100%	章/本	
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力	碩士生	0	0	100%	人次	

	（外國籍）	博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		
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。)		本研究呈現經前不悅症敵意症狀隨月經起伏之現象，並證實行為反應特質，情緒適應能力，與注意力對敵意症狀有顯著影響。除此之外，亦證實經前不月症與廣泛性焦慮症之共病。同時，在有限經費下完成有關經前不月症婦女之腦功能性連結研究，呈現經前不悅症婦女於 cadate and insula 之連結變異。目前完成資料統整，預備投稿中。					

	成果項目	量化	名稱或內容性質簡述
科教處計畫加填項目	測驗工具(含質性與量性)	0	
	課程/模組	0	
	電腦及網路系統或工具	0	
	教材	0	
	舉辦之活動/競賽	0	
	研討會/工作坊	0	
	電子報、網站	0	
	計畫成果推廣之參與（閱聽）人數	0	

科技部補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■達成目標

□未達成目標（請說明，以 100 字為限）

□實驗失敗

□因故實驗中斷

□其他原因

說明：

2. 研究成果在學術期刊發表或申請專利等情形：

論文：□已發表 □未發表之文稿 □撰寫中 ■無

專利：□已獲得 □申請中 ■無

技轉：□已技轉 □洽談中 ■無

其他：（以 100 字為限）

研究結果充分，但因剛完成收案，資料整理中，尚未完成投稿。

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）（以 500 字為限）

本研究完成 97 名 PMDD 個案及 65 名控制組之研究與分析，本研究針對易怒症狀進行分析，呈現其於月經週期顯著之變化，同時，進一步探討行為反應模式，情緒控制型態，及注意力於敵意上之角色。結果支持 freeze response to aversive stimuli, impaired affection adjustment, 及 inattentive behavior 與易怒相關，可作為進一步處理易怒症狀之依據。同時，也顯對嫌惡刺激的反應模式，情緒控制型態及認知功能需要有深入的評估，以進一步了解經前不悅症之機轉。除此之外，本研究已發現 PMDD 患者於腦結構與功能性連結上之變異。其中，PMDD 婦女有較高之 cadate-insula connectivity，此可能顯示，PMDD 婦女之行為選擇，容易受到情緒生理反應之影響。進一步比較 functional connectivity 於經前與精後之影響，結果顯示 PMDD 婦女於經前 caudate 與 anterior cingulate 有較高之連結。除此之外，insula 間亦有較高之連結。這些研究結果顯示，經前不悅症婦女之功能性連結於經前有顯著的變異，顯示經前不悅症狀一系列情緒認知行為之症狀，可能與月經週期間之腦功能變異有關，值得進一步之研究。