行政院國家科學委員會專題研究計畫 期末報告

經前不悅症之基因多型性、生理因子、腦影像學與精神病理學研究(重點代號:GM07)(第 2 年)

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中文摘要： 經過診斷會談後，再追蹤兩個月，本研究共計有 67 名個案區分為 PMDD 組，75 名個案區分為對照組經。在問卷結果中，不論是核心症狀、憂鬱、敵意、焦慮、食慾、行為抑制、壓力反應 PMDD 組與對照組都有顯著差異，同時也都有明顯前惡化之傾向。基因多行性分析顯示，。除此之外，經前不悅症組有顯著之飲食失控，情緒性飲食，及食物渴求之現象，這些現象均有顯著經前惡化之傾向。基因分析結果顯示，Serotonin 1A Receptor and Estrogen Receptor α Genes 之基因多型性與經前不悅症有顯著相關，結果顯示在帶有 G allele of ESR1-XbaI 的個案中，GG genotype of serotonin IA receptor 之個案有 4.8 倍罹患機前不悅症之風險。此結果驗證，經前不悅症同時受到血清素及女性荷爾蒙相關基因多型性之影響。除此之外，經前有認知功能缺損(工作記憶與反應抑制)之表現，此表現不僅表現在與對照組之差異，亦表現在經前與濾泡期之差異。同時，也受到上述基因多型性之影響，此結果顯示，認知功能同時後到生理及體質因素之影響，而非單純的情緒因素。同時，影像學研究亦驗證，進行工作記憶時，經前不悅症組有較低之活性，同時，經前不悅症組於經前有較低之活性，這些結果顯示，經前不悅症認知缺陷之腦活化機轉。除此之外，本研究意顯示經前不悅症個案有明顯之食慾渴求，除此之外無法抑制食慾與失控的飲食均有明顯的經前惡化傾向，同時，影像學研究亦顯示再食物圖片的誘發下，於 insula, precuneus,及 parahippocampus 等相關位置，有顯著較高之活化。此結果呈現經前不悅症食慾變化之神經生物心理機轉。本研究藉由整合精神病理、影像醫學、基因多型性、及女性荷爾蒙之研究方法，完成對經前不悅症較為完整的探討與分析。

中文關鍵詞： 經前不悅症, 黃體素, 雌激素, 食物渴求, 認知功能，基因多型性

英文摘要： A total of 67 women with PMDD and 75 controls were recruited based on the psychiatric diagnostic interviewing and two-menstrual cycle follow-up. The behavior evaluation demonstrated that women with PMDD have higher depression, hostility, anxiety, food craving, behavior inhibition, and stress than the control group. Further, these associated symptoms exacerbated significantly in the premenstrual phase. The polymorphism analysis demonstrated that the interaction term of 5-HT1A and ESR α-XbaI significantly predicted the risk of PMDD. Stratified

analysis suggested that subjects with the GG genotype of 5-HT1A had a 4.82-fold increased risk of PMDD than C carriers of 5-HT1A among G carriers of ESR α-XbaI. Furthermore, the interaction term of 5-HT1A and ESR α-XbaI also predicted the severity of premenstrual symptoms and cardinal symptoms, such as depression and irritability, in the premenstrual phase. Cognitive analysis demonstrates the premenstrual decline of WM and cognitive control among women with PMDD. The GG genotype of HTR1A (rs6295) associated with poorer premenstrual WM. Further, GG genotype of HTR1A (rs6295) determine the vulnerability to the menstrual effect and PMDD effect on cognitive function. The brain imaging analysis demonstrated that women with PMDD have a lower brain activation over superior frontal lobe than control group when processing working memory. On the other hand, women with PMDD have a lower brain activation over posterior cingulate/precuneus in premenstrual phase than follicular phase when processing working memory. This also support the working memory deficit vulnerable to the effect of menstrual cycle. y using integrated analysis of behavior, cognitive, hormone, and imaging data, this presenting study demonstrated a possible psycho-neuro-endocrine mechanism of PMDD.

英文關鍵詞： PMDD, progesterone, estrogen, working memory, food craving, polymorphism.

壹. 研究背景

經前不悅症 (premenstrual dysphoric disorder, PMDD) 近幾年來逐漸被重視，研究顯示 3-8%之育齡婦女達到經前不悅症之診斷標準。此疾病不僅帶來心理與生理上之症狀，更嚴重影響生活品質，需要積極的介入來避免其負面影響。經近幾年之積極研究，於診斷及治療上已逐漸形成共識。但有關經前不悅症之致病機轉，目前仍未有完整之結論，經前不悅症之臨床特點在於其包含許多不同層面之生理與心理症狀，包括易怒、憂鬱、食慾變化、及認知功能變化。所以，一方面其具備許多其他疾病之典型表現，但不同的卻是在濾泡期可以有明顯之改善，故其具有十分特殊而難以釐清之致病機轉，亟待完整的研究來加以釐清。過去針對經前不悅症在基因多型性、精神病理學、荷爾蒙及認知行為科學上，已有諸多之研究，但由於缺乏整合，導致難以提出完整之解說。雖然目前針對經前不悅症最常提及的假說包括荷爾蒙理論 (雌體素下降)、血清素理論(血清素功能失調)、以及共病理論(近似憂鬱症)，但均未能完整的解釋經前不悅症之表現。除此之外，過去研究著重於憂鬱症之調查，對於食物渴求 (food craving)、易怒 (irritability)、衝動 (impulsivity)、認知功能 (cognitive function)、及其他共病症狀，相關研究顯有不足，這些症狀除造成個案直接之生理或心理痛苦外，易造成個案生活功能之影響（人際問題），甚至可能導致健康問題(如肥胖)，若未能加以了解來提供有效的治療，將導致社會功能之研究影響。故本研究之目的在於整合基因多型性、精神病理學、荷爾蒙分析、及神經影像科學來完整的探討經前不悅症之機轉（著重於血清素與憂鬱症機轉），並針對食物渴求、易怒、衝動、認知功能、及其他共病症狀，做更深入之分析，以期作為發展經前不悅症有效及完整治療之依據。

貳. 文獻回顧

一. 經前不悅症：

1. 概論：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。同時，也有食慾改變、失眠等不適之生理症狀。受經前不悅症所苦之婦女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，增加了直接的醫療支出，同時造成工作產能之下降，並造成非直接的經濟影響 (Mishell, 2005)。

二. 經前不悅症仍需進一步釐清之研究議題:

1. 與憂鬱症及血清素間之關連：依據上述的文獻回顧，與憂鬱症及血清素之關連仍存在以下幾個研究議題:
   (1) 經前不悅症是否為憂鬱症之亞型，除了需要確認經前不悅症個案於濾泡期之憂鬱症狀是否高於對照組，亦須進一步評估是否符合憂鬱診斷。但本團隊過去研究顯示，濾泡期之憂鬱症指數的確高於對照組，但其平均分數未超過量表之切分點。但除了主觀的評估外，若針對經前不悅症之神經生理反應，例如 fMRI，來觀察是否存在與憂鬱患者相同的神經生物反應，亦可進一步釐清其與憂鬱患者之神經生物機轉是否一致，將有助於釐清經前不悅症之致病機轉。過去研究曾以 fMRI 觀察經前不悅症 emotional gonogo 之反應 (Protopopescu et al., 2008)，但其並非憂鬱症最重要之神經生物機轉，如可針對 emotional process 進行觀察，也助於了解經前不悅症之憂鬱機轉，並可與過去憂鬱症之結果進行比較。
   (2) 血清素所扮演之角色:過去研究顯示 acute tryptophan depletion 可於經前不悅症患者誘發憂鬱症狀。但血清素相關基因多型性卻未有相關，除可能是基因經由多基因模式影響或經由與環境交互作用影響而無法發現單一影響之基因外，亦可能與基因多型性的選擇有關

外，同時亦可能與個案數有關。故宜適當的參考過去顯著研究，以推論實際可行之個案數，進行血清素相關多型性之研究，來印證經前不悅症之血清素理論。

2. 雖然過去有關經前不悅症過去有相當多的發表，但絕大多數著重於與憂鬱症之關聯與血清素因素的探討。然而，針對經前不悅症許多其他的症狀，則缺乏詳細與完整之研究，而經前不悅症合併許多不同層面的症狀和臨床表現，這些特性之機轉仍須進一步之研究。

(1) 食物渴求與肥胖：過去僅有一研究提及經前不悅症與肥胖之關聯(Masho, Adera, & South-Paul, 2005)，除此之外，本研究結果亦顯示，經前不悅症患者於黃體期有較高之BMI(Yen et al., 2010)，並有明顯之食物渴求現象，尤其對於甜食，有顯著之情緒反應與渴求反應。而此食物渴求，在控制年齡與教育程度後，與肥胖有顯著相關。此結果顯示，經前不悅症患者可能是肥胖之高危險群，但於經前不悅症之症狀中，除食物渴求外，憂鬱、敵意與衝動皆可能與肥胖有關（本研究團隊發表中之資料），但食物渴求是這些關聯之中介因子，此結果顯示食物渴求是經前不悅症肥胖之重要因素之一。但，為何經前不悅症之患者於月經前會有明顯之食慾變化？過去許多研究有不同之結果，月經週期曾被認為與食物渴求有關，但許多研究顯示，此現象於經前不悅症患者更為明顯(Reed, Levin, & Evans, 2008; Yen et al., 2010)。但確切因素與機轉為何，則未有深入之瞭解。由於肥胖與食慾涉及生理、心理、與荷爾蒙因素(Berthoud & Morrison, 2008)，其重要控制機轉包含：下視丘與腦幹（因生理需求誘發食慾）、酬償系統（以酬償反應誘發進食行為）、腸道荷爾蒙（如 Ghrelin 等）、及週邊脂肪訊息（如 leptin）。除此之外，其相關因素包含憂鬱（emotional eating 之機轉）、月經週期、人格特質（impulsivity or lack of self control）等諸多因素(Suzuki, Simpson, Minnion, Shillito, & Bloom, 2010)。尤其進入商業年代，食物本身的誘發性亦成為另一重要因子。然而，經前不悅症之食慾轉變最大之特性在於黃體期之惡化。但，針對其食慾轉變之機轉，目前所知十分有限。故除了臨床食慾症狀的評估，更有需要整合基因多行性（與神經傳導物質相關）、功能性磁振造影（腦生物因子）、荷爾蒙分析、及臨床之觀察進行完整的調查，以深入探討經前不悅症患者食慾渴求 bio-psycho-social 之整合因素，以瞭解經前不悅症肥胖及食物渴求可能之機轉，並作為治療與預防肥胖之依據。

(2) 認知功能變化：研究者於過去之國科會研究結果發現，經前不悅症患者於經前之複雜工作記憶有顯著之下降，但於黃體其則沒有差異（under submission）。與 Reed 等人之研究結果一致(Reed et al., 2008)，同時，工作記憶下降與易怒及無法專心有關。但，截至目前為止，經前不悅症患者與經前工作記憶下降之機轉仍未瞭解。除了過去研究對於認知功能之評估較為簡略，同時有關認知功能下降是因為神經傳導物質之變化，或是腦神經生物機轉，亦或是荷爾蒙之影響，尚未有深入之研究。固有需要針對工作記憶相關之基因多行性、腦活化表現、及各項荷爾蒙之變化進行深入的瞭解，除可釐清相關機轉，以可提出整合性之解釋模式。

(3) 衝動控制問題：研究者於過去之研究亦發現，經前不悅症患者，有較高之衝動控制問題（submission to CNS spectrum, under secondary evision）。同時，這樣的問題存在於黃體期及濾泡期。這是第一個注意到經前不悅症患者衝動控制問題之研究結果。但，僅是問卷的評估，缺乏其他客觀之評估方式，若能以認知測驗或功能性磁振造影做進一步之觀察，將有助於了解衝動控制缺陷之機轉。

(4) 情緒障礙：經前不悅症最主要之情緒表現為憂鬱與易怒，憂鬱是最常被討論的共病問題之一，但憂鬱症狀是否於濾泡期緩解一直是定義與觀察結果爭議之問題 (De et al.,

2005)。而易怒是另一個重要之表現。除此之外，研究者於過去之研究結果亦發現，經前不悅症與泛焦慮症有顯著之共病現象。這些結果顯示，經前不悅症和許多情緒症狀均有著顯著的關聯，尤其過去研究顯示，經前不悅症與壓力症狀及荷爾蒙有關(Yamamoto, Okazaki, Sakamoto, & Funatsu, 2009; Cahill, 1998)。所以，這是否顯示，經前不悅症於黃體期對情緒的因應和反應能力可能有顯著之障礙，然而，除了問卷的研究，過去研究未曾針對情緒因應的腦神經機轉、或神經傳導物質因素進行深入之瞭解。若可進一步以功能性磁振造影觀察情緒處理之腦活化表現，除有助於釐清經前不悅症情緒障礙之神經生物機轉，亦有助於了解其與憂鬱症或其他壓力因應障礙腦神經機轉之異同。

3. 基因多型性之整合:依據 Poiana 等人之回顧，認為經前不悅症可能涉及各種不同神經傳導物質的機轉，故針對經前不悅症之基因多型性需要有更廣泛的研究，然於有限之資源下如何做有效的運用，本研究回顧與經前不悅症相關症狀有普遍關聯之基因多形性，作為本研究之研究標的，這些基因包括:

   (1) 與 Estrogen receptor 相關之基因： estrogen receptor alpha gene 曾多次被發現與經前不悅症有關。本研究將進一步分析該基因對共病症狀，認知功能，與神經生物反應(fMRI)反應之關聯。

   (2) 與 serotonin 有關之基因多型性: 5-HTTLPR, 5-HTR1A, Tryptophan hydroxylase 1 及 MAOA

      A. 5-HT transporter gene (SLC6A4) promoter polymorphism (5-HTTLPR): 是最常被報告與憂鬱症有關之基因之一，同時，亦與衝動控制問題有關(Verdejo-Garcia, Lawrence, & Clark, 2008; Savitz & Drevets, 2009; Way & Lieberman, 2010)。

      B. 5-HTR1A: 亦是血清素重要基因多型性之一，同時被認為與有憂鬱症以及衝動控制有關(Benko et al., 2010; Way & Lieberman, 2010)。

      C. Tryptophan hydroxylase 1 (TPH intron 7 A218C polymorphism):與血清素之生成有關，其影響血清素之合成，曾被報告與憂鬱症、成癮疾患、以及人格特質有關。

      D. MAOA(30-bp variable nucleotide tandem repeat):曾被報告與憂鬱症、社交敏感、及衝動控制有關(Passamonti et al., 2006; Kinnally et al., 2009; Savitz & Drevets, 2009)。

   (3) 與 Norepinephrine 有關之基因：研究者於過去研究發現經前不悅症與泛焦慮症之共病現象，亦發現焦慮是經前不悅症經常出現之症狀之一，故本研究亦針對泛焦慮症進行評估，而基因多型性方面，Norepineprine 一直被認為與焦慮症有關，故本研究亦分析經前不悅症與 norepineprine 基因多型性之關聯。

      A. Alpha-2A adrenergic receptor(ADRA2A): 此基因多型性與衝動、激動、敵意有關 (Levy, 2008; Prestes, Marques, Hutz, Roman, & Bau, 2007; Comings et al., 2000)。

      B. Dopamine β hydroxylase (DBH) genetic polymorphism rs2519152: 其生理角色在於將 dopamine 轉為 norepinephrine，其與衝動有關(Hess et al., 2009)。

   (4) 與壓力反應有關之基因:本研究針對與壓力因應有關的四個生肽相關之基因多型性進行調查，包括 CREB, BDNF, CRF and PDNY。

      A. c-AMP response element binding protein (CREB): 是一個影響 trascription 之蛋白質，同時與壓力相關，被認為是影響壓力的重要機轉之一(Briand & Blendy, 2010)。

      B. Brain-derived neurotrophic factor (BDNF) val66met polymorphism：BDNF 於壓力反應扮演重要之角色 (Briand & Blendy, 2010; Pardon, 2010; Ghitza et al., 2010)。

      C. Corticotropin-releasing factor（CRF）: CRF 之作用為促進 ACTH 之釋放，而影響 cortisol

之分泌 (Briand & Blendy, 2010)。

D. Prodynorphin gene (*PDYN*) promoter: dynorphin/kappa opioid system 被認為在壓力反應上扮演後端關鍵的角色(Briand & Blendy, 2010; Bruchas, Land, & Chavkin, 2010)。

參.研究目的：

由前述回顧可以瞭解，經前不悅症十分複雜，同時包含許多層面之症狀，除身體症狀外，尚包括憂鬱、易怒、注意力下降、疲勞、食慾變化等症狀，所以，這些症狀是來自於經前不悅症本身之症狀，或是只是經前症狀惡化原本之精神疾患，目前仍難以確認。除此之外，經前不悅症之病因雖然以雌體素假說及血清素假說為主，但到目前為止，確切之機轉仍未確認。故本研究之目的分為兩個部份：

1. 於研究方法學上，本研究運用整合性研究知方式，針對經前不悅症進行完整之調查。本研究預計整合基因多型性、精神病理學、神經影像學、生理學(荷爾蒙)、認知測驗、及行為量表之研究方法，完整的探討有關經前不悅症可能之病因學。
2. 本研究並針對經前不悅症之特殊表現及影響進行完整之評估，除瞭解其表現外，亦進一步探究基因多行性對特殊症狀與這些共病症狀之關聯，尤其是對這些症狀相關的腦功能表現之影響。研究之主要目標包括：

(1) 食物渴求與肥胖

(2) 衝動控制

(3) 敵意

(4) 工作記憶缺陷（臨床表現為無法專心）

(5) 壓力反應

A. 徵求對照組條件包括：

a. 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。

b. 在月經週期來之前一週於上述十一個症狀具有 2 項以下，或超過兩項但十分輕微不會造成困擾：

B. 本研究之排除條件:

a. 懷孕或可能懷孕

b. 服用任何之 psychotropic medication、避孕藥及非法藥物。

c. 罹患可能導致身體危險之重大生理疾患

d. 合併智能障礙、精神病性疾患、自閉症、或器質性精神病等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。

C. 研究人數：目前共計收案

一. 施測工具：

(1) 診斷性會談工具:

A. 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。

B. 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。

(2) 功能性磁振造影:

A. 以 3DSPGR 之方式收集結構影像，除供定位之用，亦作為活化結果呈現之版模。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)，以 8 分鐘之時間，收集靜止 EPI 之訊號，以分析 default model。

B. 針對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。

C. 功能性磁振造影之行為測驗(以 presentation 軟體設計)

a. Cue induced craving paradigm：依據 cue induced carving model，參考本團隊過去使用之 event related design，共計使用 60 張甜食及肉食照片作為刺激線索，兩種各取 30 張經反轉與馬賽克處理至無法辨識，做為 neutral stimulation。經 pseudorandom 排列，以每張顯示兩秒，間隔時間 jittered 為 3-8 秒。同時，在進行研究前後，請個案填寫本刺激模式在誘發食物渴求反應，藉此呈現食物渴求之腦反應。

b. N back task:本研究預計以 N 2 back 作為測量工作記憶之工具。本測試分別進行 N0(看到 0 需按鈕)與 N2back task（當看到曾於間隔兩次前出現之數字重複出現時需按鈕：eg. 0-1-2-4-**2**-按鈕）及 N3 back task，以 block design 設計，以 N2 back block – N0 back block 及 N3 back block – N0 back block 代表低難度與高難度之工作記憶之腦功能。

c. Go/Nogo Paradigm: 以 0-5 之數字為刺激，每個數字出現 0.2 秒間隔 1.03 秒（以製造 jittering），告知個案看到數字需盡快的按鈕，但是看到 2 不可按，預計進行 480 個 trials，其中有 80trials 不可按。本研究將紀錄受試者之 reaction time, commission error, and remission error。本研究以 Go/Nogo 作為觀察 response inhibition 之工具，主要以 commission errors 之次數為指標，commission errors 越高，代表越嚴重的 response inhibition 缺陷，此亦代表 impulsivity 之特質。於此研究中，利用（Nogo trials）-（Go trials）可以獲得進行 response inhibition 之腦活性，以瞭解那些腦位置在 response inhibition 扮演重要之角色。

d. 情緒處理測驗（emotion processing task）：以 event related 之方式設計，選取負面情緒（憂鬱）、正面情緒、敵意情緒、中性情緒四種照片各 60 張，以 pseudorandom 知方式呈現，藉由對情緒反應之大腦活化，來瞭解 PMDD 於經前憂鬱與敵意之神經生物機轉。

(3) 基因分析：篩選與憂鬱、敵意、衝動、食慾或認知功能機轉有關之神經傳導物質（如 dopamine, serotonin, norepinephrine）之基因多型性。包括:

A. 與 Estrogen receptor 相關之基因：The estrogen receptor alpha gene

B. 與 serotonin 有關之基因多型性: 5-HT transporter gene (SLC6A4) promoter polymorphism (5-HTTLPR)；5-HTR1A；5-HTR2A；Tryptophan hydroxylase 1(TPH intron 7 A218C polymorphism) & 2

C. 與 dopamine 有關之基因多型性: Catechol-O-methyltransferase Val(158)Met Polymorphism (COMT)。

D. 與 Norepinephrine 有關之基因：Alpha-2A adrenergic receptor(ADRA2A)； Dopamine β

hydroxylase (DBH) genetic polymorphism。

E. 與 Monoamine 有關之基因多型性: MAOA, MAOA VTNR

F. 與壓力反應有關之基因: c-AMP response element binding protein (CREB)；Brain-derived neurotrophic factor (BDNF) val66met polymorphism；Corticotropin-releasing factor （CRF)；Prodynorphin gene (*PDYN*) promoter。

(4) 生理因子評估:

A. 月經相關荷爾蒙：estrogen, progesteron, LH, FSH

B. 與食物渴求相關荷爾蒙：Leptin, Grelin（進食前後調查）

C. BMI 調查

(5) 自填問卷：

A. 有關經前不悅症之調查

a. 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。

b. 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，以追蹤 2 個月的時間，以確認診斷。

B. 有關共病精神症狀之調查

a. 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越高代表憂鬱程度越高。(Yang et al. 2004)。

b. Penn state worry questionnaire (PSWQ)：用來評估焦慮程度，為五分 Likert's sclae，共計 16 題，用來作為評估 general anxiety disorder 之工具。

c. Perceived stress scale: 由 Cohen 等人發展，本研究使用為 10 題版，本測驗用來測量個案當下所感受到之壓力。內在信度為 0.84-0.86(61)。

C. 有關食物渴求之調查:

a. The Yale Food Addiction Scale 為參考 DSM-IV 物質依賴診斷準則所發展，用以評估食物渴求之程度。本研究用以評估食物渴求之程度。

b. Three-Factor Eating Questionnaire (TFEQ) R18: 由 Karlsson 等人發展，用以評估進食行為之相關因素。本研究用以進一步分析進食行為可能之因素。

c. 每日卡路里進食量回溯調查。

d. 視覺食物渴求調查：受試者針對 30 張食物圖片勾選進食動機之程度。

D. 有關易怒(irritability)之調查

a. 簡氏中文敵意量表：本量表共計 20 題，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。

E. 有關衝動(impulsivity)之調查:

a. The BAS/BIS Scales:由 Carver 建構之 BIS/BAS scales，其內在效度介於 0.66-0.76 間，本研究中用以測量現實情境中個案之衝動及控制特質。(Carver & White, 1994)

b. Barratt Impulsiveness Scale (BIS11)(Patton, Stanford, & Barratt, 1995): 由 BIS 10 修改而來，用以測量衝動控制，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。

F. 其他共病問題

a. 中文網路成癮量表：由陳淑惠教授所發展，量表共計 26 題，內部一致性介於 0.79-0.93 之間，兩週之再測信度為 0.83。該量表用以測量網路成癮疾患之嚴重程度。

(6) 神經認知工具：

A. Continuous performance task：進行持續之注意力測驗，受試者於 1 後面出現 9 需立即按鈕，共計 240 個 trials，其中 14 個 trials 需立即按鈕，據本研究假設，經前不悅症患者若於經前有較明顯之注意力缺陷，則經前不悅症患者於經前在此測驗應該有較高之錯誤率，同時，相對於控制組，錯誤率亦較高。

B. Go/Nogo task:以 Go/Nogo task 做為測量 response inhibition 之工具。

C. N back task:以 N2 back task 作為測量工作記憶(working memory)之工具。並於第二階段搭配食物圖片作為背景，以測驗是否對食物圖片具顯著之 attention bias。

二. 研究步驟

1. 各項研究工具製備，進行各問卷之信校度調查，完成認知測驗之再測信度，確認各項 fMRI 之 task 可誘發充分腦活性轉變，以完成各項研究準備，並張貼廣告徵求受試者。
2. 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、減肥藥或非法藥物個案，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。
3. 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。
4. 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期各進行一次測驗(認知測驗、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。
5. 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。
6. 黃體期評估：(食物渴求相關問卷均於飽食下評估)
   (1) 評估當天，請受訪者先進食(食物自備)，進食後 1 小時內填寫食物渴求問卷。
   (2) 其他問卷評估：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。
   (3) 認知測驗：Continuous performance task, Go/Nogo task, 及 N back task
   (4) 進行生理因子評估（身高體重與抽血）
7. 濾泡期評估：(食物渴求相關問卷均於飽食下評估)
   (1) 評估當天，請受訪者先進食(食物自備)，進食後 1 小時內填寫食物渴求問卷。
   (2) 其他問卷評估：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。
   (3) 認知測驗：Continuous performance task, Go/Nogo task, 及 N back task
   (4) 進行生理因子評估（身高體重與抽血）
8. 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，提醒首訪者完成「經前症狀週評估追蹤簡易問卷」，**持續追蹤兩個月的時間，以確認診斷**。
9. 完成上述研究後，於 PMDD 組與對照組依據 fMRI 受試者之條件，各篩選適當受試者，於經前及經後在飽食狀態下完成抽血之生理檢驗後，各進行一次 food cue induced craving

paradigm 之功能性磁振造影掃描。然後，於經前及經後各針對 N back task, Go/Nogo task 進行 fMRI 研究（每個 Task 進行一次 fMRI），實行時間須間隔兩週以上，依據適當之篩選條件，每個 task 須完成研究組與對照組各 25 名（共計 4 個 task）。

肆. 研究結果與討論:

研究個案確認：本研究採取嚴格的研究個案認定，經由海報徵求未經治療之經前不悅症個案，經助理依海報公布之標準，共計收集 PMDD 個案 90 名，無明顯 PMDD 病史及症狀個案 78 名。先進行 PSST 之問卷篩選，共計有 86 名 PMDD 個案符合篩選標準分為 PMDD 組，75 名未達區分標準分為對照組，其餘個案排除。再進行診斷性會談，有 83 名 PMDD 個案符合 DSMIV 診斷標準，75 名控制組個案未達診斷標準。然後，兩組個案各均分一半，一半個案於經前接受第一次測驗，另一半個案於經後接受第一次測驗(一個月經週期中接受兩次測驗)。並於測驗後以自填問卷追蹤兩個月，於追蹤的兩個月中，PMDD 組之 PMDD 分數於經前需高於對照組平均分數加兩個標準差，同時，經前症狀分數需比經後症狀分數高出 30%。符合此兩要件之個案，才區分為最後之 PMDD 組。最後，共計有 67 名個案區分為 PMDD 組，75 名個案區分為對照組。

重點研究結果:

I. 基因研究: The Interaction between Polymorphism of Serotonin 1A Receptor and Estrogen Receptor α Predicts Premenstrual Dysphoric Disorder (submitting to hormone and behavior under reviewing)

A. Result: The results demonstrated that the women with PMDD had greater PMDD symptoms, depression and irritability in the premenstrual phase. The severity of PMDD symptoms, depression and irritability increased significantly in the premenstrual phase among the women with PMDD (Table 1). Repeated measures two-factor ANOVA demonstrated premenstrual exacerbation of PMDD symptoms (F = 137.97, p < 0.001), depression (F = 29.31, p < 0.001) and irritability (F = 25.56, p < 0.001), among the women with PMDD. These results demonstrated that the PMDD group represented the clinical characteristics of PMDD based on the DSMIV-TR(Association., 2000). Chi-square analysis demonstrated no association between 5-HT_{1A} or ESR α-XbaI and PMDD diagnosis (Table 1). However, logistic regression analysis demonstrated that the interaction term of 5-HT_{1A} (G/G versus G/C+C/C) and ESR α-XbaI (G/A+G/G versus A/A) significantly predicted the risk of PMDD (OR = 8.02, 95% CI: 1.80-35.80; table 2). Further stratified analysis demonstrated that the typing of 5-HT_{1A} was associated with PMDD diagnosis (X^2 = 6.68, p <0.006; table 3) among G carriers of ESR α-XbaI, but not among those with the AA genotype. Further logistic regression analysis demonstrated that subjects with the G/G genotype of 5-HT_{1A} were at higher risk of PMDD (Wald X^2 = 6.34, OR = 4.82, 95% CI: 1.42-16.40; Table 2) than other subjects among G carriers of ESR α-XbaI. This result indicated that the genotype of ESR α-XbaI plays a moderating role in the predictive effect of the G/G genotype of 5-HT_{1A} for the risk of PMDD. Further univariate analysis of variance for PMDD symptoms, assessed by the PSST, CESD, and BDHIC-SF, demonstrated that the interaction term of 5-HT_{1A} and ESR α-XbaI is significantly associated with the severity of PMDD symptoms (F = 7.17, p = 0.008, η^2 = 5.0%), depression (F = 10.07, p = 0.002, η^2 = 6.9%) and irritability (F = 6.75, p = 0.01, η^2 = 4.7%). Further stratified analysis demonstrated that subjects with the G/G allele of 5-HT_{1A} had a greater severity of PMDD symptoms, depression and irritability, in the premenstrual phase than others among G carriers of ESR α-XbaI, but not among those with the A/A genotype (Table 3). This result supports that the genotype of ESR α-XbaI plays a moderating role in the association between G/G genotypes of 5-HT_{1A} and the severity of PMDD symptoms in

the premenstrual phase.

Table 1. The associations between polymorphisms of serotonin 1A receptor (5-HT_{1A} C(-1019)G) and estrogen α receptor (ESRα-XbaI) and premenstrual dysphoric disorder (PMDD) and the characteristic presentation of the PMDD group.

Variables	PMDD Case (N=66) N(%) or (Mean ± SD)	Paired t test	Control (N=74) N(%) or (Mean ± SD)	Paired t test	*t* or X^2
5-HT_{1A} C(-1019)G					
G/G (N=84)	41 (62.1%)		43 (58.1%)		0.23
G/C & C/C (N=50;6)	25 (37.9%)		31 (41.9%)		
ESRα-XbaI					
AA (N=92)	40 (60.6%)		52 (70.3%)		0.82
GA & GG (N=43;5)	26 (39.4%)		22 (29.7%)		
Age	23.36 ± 3.13		23.62 ± 3.51		-0.46
Educational level	16.09 ± 1.15		16.27 ± 1.75		-0.71
Premenstrual symptoms	40.56 ± 6.41		20.07 ± 4.21		22.07***
PMDDSQ(P)	78.44 ± 15.81	14.68***	16.20 ± 15.27	5.18***	22.67***
PMDDSQ(F)	27.56 ± 23.27		8.24 ± 12.07		6.06***
Depression(P)	27.58 ± 10.02	5.92***	10.43 ± 6.36	0.84	11.92***
Depression(F)	18.09 ± 12.62		9.91 ± 6.06		4.80***
Irritability(P)	64.86 ± 14.22	5.77***	46.15 ± 10.92	0.39	8.65***
Irritability(F)	54.73 ± 15.47		45.78 ± 10.12		4.00***

Premenstrual symptoms: assessed by The Premenstrual Symptoms Screening Tool; PMDDSQ: The premenstrual dysphoric disorder (PMDD) severity questionnaire; P: premenstrual phase; F: follicular phase; Depression: score of the Center for Epidemiological Studies' Depression Scale; Irritability: score of the Buss-Durkee Hostility Inventory- Chinese Version- Short Form.
SD: standard deviation. ***: p<0.001

Table 2. The predictive value of the interaction term of serotonin 1A receptor C(-1019)G (*HTR1A* rs6295) and estrogen α receptor (*HTR1A* rs6295) for the risk of PMDD and further stratified analysis.

Logistic regression for PMDD	Wald χ^2	Odds ratio	95% CI
HTR1A rs6295 [G/G]	1.34	0.60	0.25-1.42
HTR1A rs6295 [G carrier]	1.52	0.50	0.17-1.50
HTR1A rs6295 by ESRα-XbaI	7.44**	8.02	1.80-35.80
Among *HTR1A* rs6295 [A/A]			
HTR1A rs6295 [G/G]	1.34	0.60	0.25-1.42
Among *HTR1A* rs6295 [G carrier]			
HTR1A rs6295 [G/G]	6.34*	4.82	1.42-16.40

*: p<0.05; **: p<0.01

Table 3. Stratified analysis by estrogen α receptor (ESRα-XbaI) to evaluate the associations between polymorphism of serotonin 1A receptor (5-HT_{1A} C(-1019)G) and PMDD diagnosis, PMDD symptoms, and logarithmic-transformed estrogen and progesterone levels.

	In G carriers of ESRα-XbaI			**In AA genotype of ESRα-XbaI**		
	5-HT_{1A} C			**5-HT_{1A} C**		
Variables	**GG (N=25) (Mean ± SD)**	**GC & CC (N=23) (Mean ± SD)**	***t* or X^2**	**GG (N=59) (Mean±SD)**	**GC & CC (N=33) (Mean ± SD)**	***t* or X^2**
PMDD						
Case	18 (69.2%)	8 (30.0%)	6.68*	23 (57.5%)	17 (42.5%)	1.35
Control	7 (31.8%)	15 (68.2%)		36 (69.2%)	16 (30.8%)	
PMDD symptoms	35.72 ± 11.28	26.48 ± 12.02	2.75**	28.31 ± 11.17	30.00 ± 11.01	-0.70
PMDDSQ(P)	60.80 ± 33.33	38.22 ± 35.41	2.28*	41.12 ± 39.94	47.00 ± 33.11	-0.79
PMDDSQ(F)	15.72 ± 15.98	16.52 ± 22.18	-0.15	20.27 ± 23.42	13.94 ± 16.85	1.37
Depression(P)	24.56 ± 12.95	13.91 ± 9.65	3.21**	17.08 ± 11.42	19.70 ± 11.90	-1.04
Depression(F)	17.68 ± 12.71	13.09 ± 11.37	1.32	12.08 ± 8.56	14.27 ± 10.95	-0.90
Irritability(P)	61.64 ± 15.62	50.17 ± 15.68	2.54*	53.29 ± 16.16	56.27 ± 13.47	-0.43
Irritability(F)	52.96 ± 15.40	46.57 ± 13.32	1.53	49.61 ± 13.86	50.85 ± 11.93	0.75
Estrogen (P)	73.49 ± 59.85	100.43 ± 44.81	-2.53*	72.07 ± 42.94	82.94 ± 57.38	-0.75
Estrogen (F)	60.19 ± 40.95	74.00 ± 61.47	-0.97	60.58 ± 48.99	59.75 ± 44.83	-0.04

*: p<0.05; **: p<0.01

PMDD symptoms: assessed by The Premenstrual Symptoms Screening Tool; PMDDSQ: PMDD symptoms assessed by the premenstrual dysphoric disorder (PMDD) severity questionnaire; P: premenstrual phase; F: follicular phase; Depression: score of the Center for Epidemiological Studies' Depression Scale; Irritability: score of the Buss-Durkee Hostility Inventory- Chinese Version- Short Form. The t value for estrogen was calculated based on logarithmic-transformed data, and one data of a C carrier of 5-HT_{1A} among the G carriers of ESRα-XbaI is missing.

Table 4. Univariate analysis of variance of the effects of polymorphisms of serotonin 1A receptor (5-HT_{1A} C(-1019)G) and estrogen α receptor (ESRα-XbaI) on the severity of premenstrual dysphoric disorder(PMDD) symptoms, depression and irritability in the premenstrual phase.

	Within-subject analysis			
Variables	**Df**	**Mean square**	**F**	**Partial Eta**
PMDD symptoms				
5-HT_{1A} C(-1019)G	1	435.66	3.41	0.024
ESRα-XbaI	1	115.94	0.91	0.007
5-HT_{1A} C(-1019)G by ESRα-XbaI	1	914.94	7.17**	0.050

PMDD depression				
5-HT_{1A} C(-1019)G	1	493.82	3.70	0.026
ESRα-XbaI	1	21.88	0.16	0.001
5-HT_{1A} C(-1019)G by ESRα-XbaI	1	1344.80	10.07**	0.069
PMDD irritability				
5-HT_{1A} C(-1019)G	1	550.26	2.32	0.017
ESRα-XbaI	1	38.83	0.16	08001
5-HT_{1A} C(-1019)G by ESRα-XbaI	1	1597.35	6.75*	0.047

*: $p<0.05$; **: $p<0.01$

PMDD symptoms: assessed by The Premenstrual Symptoms Screening Tool; Depression: score of the Center for Epidemiological Studies' Depression Scale; Irritability: score of the Buss-Durkee Hostility Inventory- Chinese Version- Short Form.

Discussion

Further analysis in this study firstly demonstrated that the interaction term of 5-HT_{1A} and ESR α-XbaI significantly predicted the risk of PMDD. Stratified analysis suggested that subjects with the G/G genotype of 5-HT_{1A} had a 4.82-fold increased risk of PMDD than C carriers of 5-HT_{1A} among G carriers of ESR α-XbaI. Furthermore, the interaction term of 5-HT_{1A} and ESR α-XbaI also predicted the severity of premenstrual symptoms and cardinal symptoms, such as depression and irritability, in the premenstrual phase. Further stratified analysis suggested that subjects with the G/G genotype of 5-HT_{1A} had higher premenstrual symptoms, depression and irritability among G carriers of ESR α-XbaI. These results indicated that polymorphism of ESR α-XbaI plays a moderating role in the association between the G/G genotype of 5-HT_{1A} and the risk and symptoms of PMDD.

The GG genotype of 5-HT_{1A} has been reported to reduce serotonin neurotransmission (Albert, Le Francois, & Millar, 2011). Because of its effect on serotonin , the GG genotype has been shown to contribute to depression and a poor response to SSRIs (Drago, Ronchi, & Serretti, 2008). Further, the effect was found to be more significant among vulnerable subjects, such as those with depression or chronic stress (Albert, 2012). Women with PMDD are vulnerable to major depressive disorder (Hartlage, Arduino, & Gehlert, 2001), and the GG genotype of 5-HT_{1A} reduces serotonin transmission and contributes to clinical symptoms, particularly depression. This mechanism might explain why the GG genotypes of 5-HT1A affected the depression score in this study. Further, a previous report suggested that SSRI treatment reduces premenstrual irritability (Landen, Erlandsson, Bengtsson, Andersch, & Eriksson, 2009), and the serotonin dysregulation associated with the GG genotype of 5-HT_{1A} might also result in irritability in PMDD, as shown in this study. Since depression and irritability are two cardinal mood symptoms of PMDD (Born, Koren, Lin, & Steiner, 2008; Landen & Eriksson, 2003), the effect of the GG genotype of 5-HT_{1A} on these symptoms would contribute to the strong risk of PMDD, which is the key result of this study. This result provides genetic evidence to support the role of serotonin dysregulation in the mechanism of PMDD(Halbreich, 2003; Rapkin & Akopians, 2012; Steiner & Pearlstein, 2000).

Dhingra and colleagues hypothesized that the G allele is associated with the occurrence of PMDD. However, their data indicated that the C/C genotype contributes to the risk of PMDD (Dhingra et al., 2007).

As the CC genotype of 5-HT_{1A} represents normal serotonin function (Albert et al., 2011), the reverse result is contrary to previous assumptions related to serotonin dysregulation in PMDD (Rapkin & Akopians, 2012). This study included a greater number of PMDD cases with characteristic presentation of PMDD and analyzed the interaction between two important polymorphisms. By the moderating effect of ESR α-XbaI, the GG genotype of the 5-HT_{1A} has been demonstrated to strongly predict the risk of PMDD. This result supports that interaction between serotonin dysregulation and estrogen function contributes to the risk of PMDD. It also suggests that the effect of estrogen function should be considered when assessing the contribution of serotonin dysregulation to PMDD.

Estrogen-serotonin interaction has been suggested to be an important mechanism of female mood disorder (Amin, Canli, & Epperson, 2005; Lokuge, Frey, Foster, Soares, & Steiner, 2011) and PMDD (Poiana, Musat, Carsote, & Chirita, 2009). Estrogen has been reported to increase the binding potential of the 5HT_{2A} receptor in cortical regions(Moses-Kolko et al., 2003) and decrease the uptake of serotonin in the serotonin transporter (Koldzic-Zivanovic, Seitz, Watson, Cunningham, & Thomas, 2004). Further, estrogen has been reported to enhance the effectiveness of SSRIs (Rasgon et al., 2002; Schneider, Small, & Clary, 2001). These results might suggest that estrogen contributes to the responsiveness of the brain to serotonin. As the GG genotype of 5-HT_{1A} results in lower serotonin transmission, a decline in estrogen in the premenstrual phase might attenuate the responsiveness of the brain to serotonin and further deteriorate the serotonin-associated mood symptoms of PMDD, such as depression and irritability. This would explain why the GG genotype of 5-HT_{1A} affects the severity of PMDD symptoms in the premenstrual phase but not in the follicular phase.

The cellular mechanism of the influence of estrogen on mood might act through the genomic mechanism(i.e., transcription factors of nuclear receptors ESR-α or ESR-beta) involving the serotonin system (Lokuge et al., 2011). ESR has been reported to participate in estrogen's enhancing effect of the antidepressant effect (Estrada-Camarena, Lopez-Rubalcava, & Fernandez-Guasti, 2006). The role of ESR in the effect of estrogen on the serotonin system might explain why polymorphism of ESRα-XbaI has been reported to contribute to the risk of depression (Ryan et al., 2012; Sundermann, Maki, & Bishop, 2010). Further, Huo demonstrated an association between haplotypes of ESR α and PMDD (Huo et al., 2007). This suggests that the gene expression of ESRα is involved in the mechanism of PMDD.

This study demonstrated that polymorphism of ESR α-XbaI plays a moderating role in the association between the GG genotype of 5-HT_{1A} and the risk of PMDD. Further stratified analysis revealed that the GG genotype of 5-HT_{1A} affects the severity of symptoms of PMDD, such as depression and irritability, and symptom exacerbation in the premenstrual phase among G carriers of ESR α-XbaI. The GG genotype of 5-HT_{1A} associates the decreased estrogen level in the premenstrual phase, which would further aggravate premenstrual estrogen withdrawal in PMDD. This study supports the previous hypothesis that both estrogen and serotonin and their interaction are involved in the mechanism of PMDD.

II. 認知功能研究: The effect of serotonin 1A receptor polymorphism on the cognitive function of Premenstrual Dysphoric Disorder (submitting to EAPCN first reviesed and under reviewing)

The analysis for the effect of PMDD diagnosis:

Women with PMDD have less successful inhibitory responses for Nogo trials, more omission errors for Go trials of Go/nogo task than controls in premenstrual phase, but not in follicular phase (Table 1, Fig 1A). Furthermore, they had lower correct hits in 2- back tasks than controls in premenstrual phase, but not in

follicular phase(Table 1, Fig 1B). Further stratified analysis showed in table 1 demonstrated that women with PMDD had lower successful inhibitory responses for Nogo trials and correct hits in 2-back tasks only among those with GG genotype of HTR1A (rs6295).

Paired *t*-test in table 1 demonstrates that successful inhibitory responses for Nogo trials and correct hits in 2- and 3-back tasks are lower in premenstrual phase than those in follicular phase among women with PMDD, but not among controls. This indicated only women with PMDD impaired cognitive control and WM in premenstrual phase. Further stratified analysis showed in table 1 demonstrated that the premenstrual cognitive decline of PMDD group is significant only among those with GG genotype of HTR1A(rs6295).

Repeated-measures two-factor ANOVA in table 2 revealed that there are interactions between the menstrual phase effect and PMDD effect for the successful inhibitory responses of Go/Nogo task ($F = 14.20$, $p < 0.001$), correct hits in 2-back task ($F = 12.21$, $p < 0.001$), and 3-back task ($F = 3.95$, $p = 0.049$). It indicated that, in comparison to control group, women with PMDD impaired more on performance Go/Nogo task, 2- and 3-back tasks from follicular phase to premenstrual phase (figure 1). These results indicate that decline in cognitive control and low- or high-demanding WM in the premenstrual phase among women with PMDD. Further stratified analysis showed in table 2 demonstrated that the premenstrual decline of Go/Nogo task ($F = 9.86$, $p = 0.002$, $\eta^2 = 11\%$) and 2-back task ($F = 11.61$, $p = 0.001$, $\eta^2 = 12.7\%$) of PMDD group is significant only among those with GG genotype of HTR1A(rs6295).

3.2 The effect of HTR1A: the direct or moderating effect to cognitive function of women with PMDD.

One woman with PMDD has missed her data of HTR1A polymorphism(rs6295). All single-nucleotide polymorphisms (SNPs) were tested for a possible deviation from the Hardy–Weinberg equilibrium (HWE ≥ 0.05) in women with PMDD or in controls. No derivation was noted for HTR1A(rs6295) (PMDD: $X^2 = 0.00$; controls: $X^2 = 0.35$). There is no significant association between genotypes of HTR1A(rs6295) to PMDD diagnosis. The limited sample sized might associate its insignificant association. The *t*-test in table 4 revealed that subjects with GG genotype of HTR1A(rs6295) had lower correct hit in 2-back task than those with G/C+CC genotype in premenstrual phase, but not in follicular phase. Further stratified analysis, demonstrate that this significant effect is found only among women with PMDD, but not among controls. The two-way ANOVA demonstrate that PMDD diagnosis ($F = 7.43$, $p = 0.007$, $\eta^2 = 5.3\%$), GG genotype of HTR1A(rs6295) ($F = 6.54$, $p = 0.012$, $\eta^2 = 4.7\%$), and their interaction term ($F = 4.47$, $p = 0.036$, $\eta^2 = 3.3\%$) were associated with lower correct hits in 2-back task in premenstrual phase.

3.3 The effect of HTR1A on premenstrual exacerbation of cognitive deficit of women with PMDD.

Paired *t*-test in table 4 demonstrates that successful inhibitory responses for Nogo trials and correct hits in 2- and 3-back tasks are lower in premenstrual phase than those in follicular phase among subjects with GG genotypes of HTR1A(rs6295), but not among C carriers (Figure 1). Furthermore, repeated-measures two-factor ANOVA in table 2 revealed that the interaction term of menstrual phase effect and polymorphism effect of HTR1A(rs6295) were significantly associated with lower correct hits in 2- back task ($F = 4.65$, $p = 0.03$, $\eta^2 = 3.4\%$). It indicated that the premenstrual exacerbation of difficulty in WM is more significant among subjects with GG genotype of HTR1A(rs6295). The further analysis demonstrate that the interaction term of menstrual phase effect, PMDD diagnosis and HTR1A(rs6295) has a trend ($F = 3.24$, $p = 0.07$, $\eta^2 = 2.4\%$) to predict the lower correct hits of 2-back task.

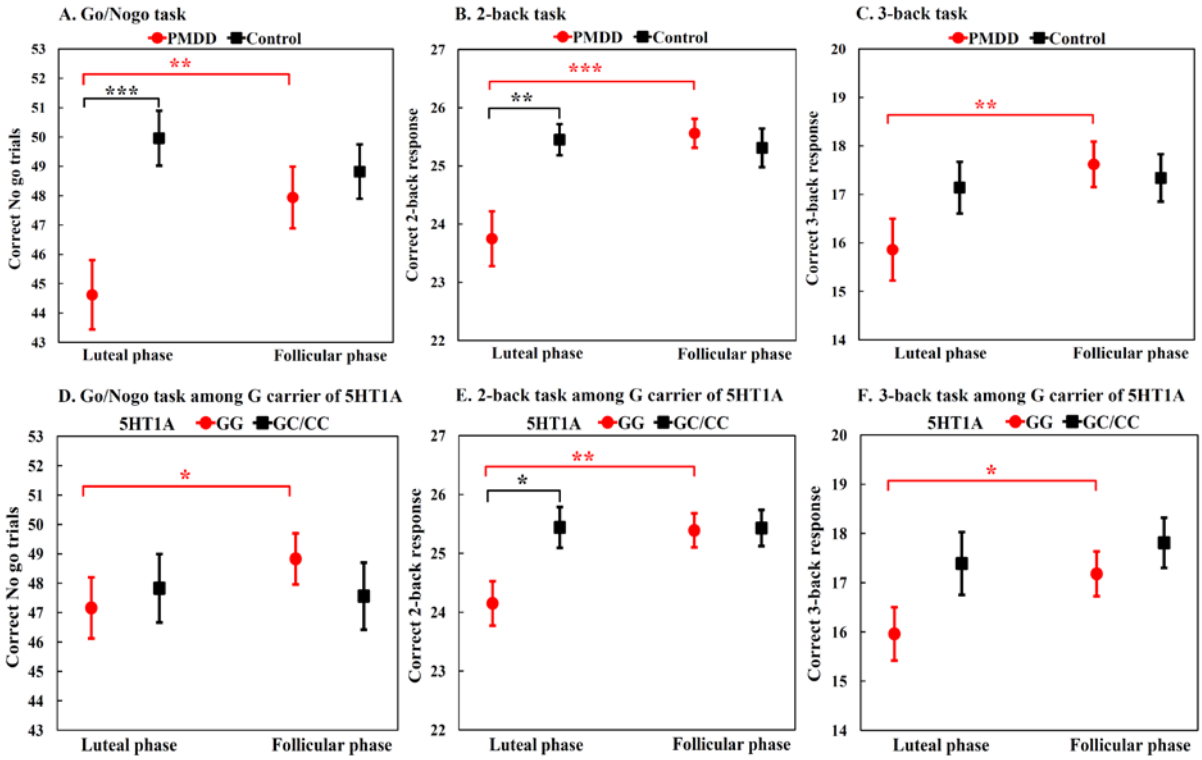


Table 1 *t*-test and paired *t*-test for performance of cognitive task between women with PMDD and controls in premenstrual or follicular phase.

	PMDD diagnosis				
Variables	**PMDD (N = 63) Mean ± SD**	**Paired *t***	**Control (N = 74) Mean ± SD**	**Paired *t***	***t***
Age	23.51 ± 3.17		23.50 ± 3.40		0.014
Education level	16.16 ± 1.17		16.24 ± 1.73		–0.329
Nogo trails (P)	44.62 ± 9.37	–3.381**	49.96 ± 8.07	1.619	–3.585***
Nogo trails (F)	47.94 ± 8.31		48.82 ± 7.98		–0.637
Omission error (P)	13.59 ± 10.09	0.648	10.11 ± 4.62	–1.640	2.521*
Omission error (F)	12.83 ± 9.78		11.55 ± 8.76		0.802
2-back (P)	23.75 ± 3.72	–3.884***	25.45 ± 2.30	0.414	–3.150**
2-back (F)	25.56 ± 1.97		25.31 ± 2.85		0.575
3-back (P)	15.86 ± 5.05	–2.846**	17.14 ± 4.59	–0.409	–1.551
3-back (F)	17.62 ± 3.71		17.34 ± 4.22		0.411
$5TH_{1A}$(rs6295) (missing value=1)	**N(%)**		**N(%)**		**χ^2 test**
G/C(N=48)+CC(N=6)	23 (42.6)		31 (57.4)		0.569
GG(N=82)	39 (47.6)		43 (52.4)		
Among GG genotype of HTR1A (rs6295)					
	(N = 39)		**(N = 43)**		
Nogo trails (P)	43.56 ± 9.81	-3.387**	50.42 ± 7.77	0.558	-3.522**
Nogo trails (F)	47.59 ± 7.90		49.95 ± 7.76		-1.366
Omission error (P)	14.72 ± 10.35	1.028	9.72 ± 4.48	-1.121	2.786**
Omission error (F)	13.51 ± 10.46		11.14 ± 8.67		1.122

2-back (P)	22.82 ± 3.99	-4.154***	25.35 ± 2.21	0.049	-3.497**
2-back (F)	25.46 ± 2.05		25.33 ± 3.07		0.238
3-back (P)	14.87 ± 5.51	-2.620*	16.95 ± 4.08	-0.514	-1.927
3-back (F)	17.05 ± 3.80		17.30 ± 4.43		-0.274

P: Premenstrual phase; F: follicular phase; Nogo trails: corrected inhibitory response in Go/Nogo task; P: premenstrual phase; F: follicular phase; Omission error: omission response in Go trails of Go/Nogo task; 2-back: correct hits in 2-back task; 3-back: correct hits in 3-back task.
*: p<0.05; **:p <0.01; ***:p<0.001

Table 2 The repeated-measure ANOVA for the interaction effect of Menstrual phase effect and premenstrual dysphoric disorder (PMDD) or serotonin receptor 1A(HTR1A; rs6295) for performance of cognitive task.

	Within-subject analysis		
Variables	**Df**	**Mean square**	**F**
The effect of PMDD diagnosis			
Corrected inhibitory response in Go/Nogo task			
MP	1	81.03	3.410
MP by PMDD	1	337.33	14.20***
Error	135	23.93	
Correct hits in 2-back task			
MP	1	47.70	9.06**
MP by PMDD	1	64.34	12.21**
Error	135	5.09	
Correct hits in 3-back task			
MP	1	65.67	6.28*
MP by PMDD	1	41.36	3.95*
Error	135	10.61	
Among GG genotype of HTR1A (rs6295)			
Corrected inhibitory response in Go/Nogo task			
MP	1	129.63	6.196*
MP by PMDD	1	206.37	9.856**
Error	80	20.92	
Correct hits in 2-back task			
MP	1	70.07	11.212**
MP by PMDD	1	72.59	11.614**
Error	80	6.25	
Correct hits in 3-back task			
MP	1	65.37	5.630*
MP by PMDD	1	34.27	2.952
Error	80	11.61	
The effect of HTR1A (rs6295)			
Correct hits in 2-back task			
MP	1	24.45	4.39*
MP by HTR1A [GG]	1	25.95	4.65*
Error	134	36.38	
The effect of interaction term of PMDD diagnosis and HTR1A (rs6295)			
MP	1	28.71	5.642*
MP by HTR1A [GG]	1	26.30	5.167*
MP by PMDD	1	43.75	8.597**

MP by HTR1A [GG] by PMDD	1	16.47	3.236
Error	132	5.09	

MP: menstrual cycle phase effect; PMDD: premenstrual menstrual dysphoric disorder.
*:p<0.05; **:p <0.01; ***:p<0.001

Table 3 The correlation between symptoms indicator of PMDD or estrogen level and performance of cognitive task in premenstrual phase.

Variables	**Nogo trials**	**2-back**	**3-back**
All subjects			
Estrogen	–0.06	–0.14	–0.14
Progesterone	–0.03	–0.12	–0.17
Estrogen change	–0.18*	–0.10	–0.07
Progesterone change	0.02	–0.08	–0.13
PMDD group			
Premenstrual symptoms	–0.434**	–0.072	–0.115
PMDD functional score	–0.409**	–0.022	0.006
Depression	–0.441**	–0.071	0.071
Irritability	–0.431**	–0.157	0.017

Nogo trails: corrected inhibitory response in Go/Nogo task; 2-back: correct hits in 2-back task; 3-back: correct hits in 3-back task; Estrogen level change: premenstrual phase–follicular phase; Progesterone change: premenstrual phase-follicular phase.
*:p<0.05; **:p <0.01

Table 4 *t*-test and paired *t*-test for performance of cognitive task between women with GG genotype of serotonin receptor 1A(HTR1A; rs6295) and C carriers in premenstrual or follicular phase.

	HTR1A (rs6295) **C(-1019)G**				
Variables	**GG (N = 82) Mean ± SD**	**Paired *t***	**G/C+CC (N = 54) Mean ± SD**	**Paired *t***	***t***
Nogo trails (P)	47.16 ± 9.40	–2.221*	47.83 ± 8.56	0.263	–0.424
Nogo trails (F)	48.83 ± 7.87		47.56 ± 8.40		0.900
2-back (P)	24.15 ± 3.41	–2.996**	25.44 ± 2.55	0.053	–2.534*
2-back (F)	25.39 ± 2.62		25.43 ± 2.26		–0.082
3-back (P)	15.96 ± 4.90	–2.265*	17.39 ± 4.68	–0.736	–1.690
3-back (F)	17.18 ± 4.12		17.81 ± 3.75		–0.906
PMDD group	**(N = 39)**		**(N = 23)**		
2-back (P)	22.82 ± 3.99	–4.15***	25.26 ± 2.73	–0.60	–2.85**
2-back (F)	25.46 ± 2.05		25.61 ± 1.83		–0.28

P: Premenstrual phase; F: follicular phase; Nogo trails: corrected inhibitory response in Go/Nogo task; 2-back: correct hits in 2-back task; 3-back: correct hits in 3-back task.
*: p<0.05; **:p <0.01; ***:p<0.001

Discussion

In line with previous studies (Reed et al., 2008; Yen et al., 2012), this study demonstrates declined WM

of women with PMDD in premenstrual phase. Furthermore, this presenting study firstly demonstrates that women with PMDD have poorer cognitive control in Go/Nogo task in premenstrual phase. These results all support that women with PMDD have impaired cognitive function in premenstrual phase. However, there is no significant difference on the performance of these tasks between women with PMDD and controls in follicular phase. This result suggests that the cognitive deficit exacerbated in premenstrual phase, remitted in follicular phase, and was menstrual-cyclic as other mood and somatic symptoms of PMDD.

Difficulty in working memory among women with PMDD.

Our result demonstrated that women with PMDD have poor working memory in the premenstrual phase. This would suggest that assistant tool which could help to keep temporal memory, such as software for thinking map or memory note, could be provided to women with PMDD to attenuate the negative effect of WM deficit to their performance in premenstrual phase. However, their WM is adequate in follicular phase. In line with previous result (Yen et al., 2012), our result support that women with PMDD have an adequate WM when they are not in the premenstrual phase.

The effect of polymorphism of HTR1A(rs6295) on working memory.

Although the role of serotonin dysregulation in WM deficit of PMDD has been suggested in previous reports (Yen et al., 2012), it has not been proved by empirical study. This present study demonstrates that GG genotypes of HTR1A (rs6295) associated with poor WM in premenstrual phase, but not in follicular phase. The two-factor ANOVA demonstrated that GG genotypes of HTR1A (rs6295) has a direct negative effect on working memory in the premenstrual phase with control of PMDD diagnosis. The G allele of HTR1A (rs6295) derepresses 5-HT1A autoreceptor expression to reduce serotonergic neurotransmission in previous report (Lemonde et al., 2003). In the depressed subjects with GG genotype of HTR1A(rs6295), HTR1A auto-receptor expression is increased, which would reduce neuronal firing and 5-HT release, while postsynaptic HTR1A receptors are reduced in certain regions, which would decrease response to 5-HT release(Albert et al., 2011). Through the effect to reduced serotonergic transmission, the GG genotypes of HTR1A (rs6295) might contribute to poor working memory as reported in this presenting study.

The interaction term of PMDD diagnosis and HTR1A (rs6295) associated with poor performance of WM in premenstrual phase. The negative effect of PMDD diagnosis on premenstrual WM was significant only among women with GG genotype of HTR1A (rs6295). It indicates that HTR1A(rs6295) moderate the effect of PMDD on poor WM in premenstrual phase, which is in line with suggestion from previous review(Su et al., 1997). Moreover, both cognitive control and WM declined in premenstrual phase only among women with GG genotype of HTR1A (rs6295). Further, the working memory declined from follicular phase to premenstrual phase more significantly among women with GG genotype of HTR1A (rs6295) than that among C carriers. It would suggest that women with GG genotype of HTR1A (rs6295) are more vulnerable to the premenstrual negative effect on working memory.

Previous study had demonstrated premenstrual deterioration in high-demanding WM among women with PMDD (Yen, et al., 2012). This study with rigorous criteria demonstrated premenstrual deterioration for both low- and high-demanding WM. Further stratified analysis demonstrate the premenstrual deterioration effect of PMDD diagnosis on WM was significant only among women with GG genotype of HTR1A(rs6295). The menstrual cyclic change on WM supports the possible role of gonadal hormone in the mechanism of WM deficit among women with PMDD. Thus, this result demonstrated that GG genotype of HTR1A (rs6295) determine the vunerability to mentrual effect on working memory among women with PMDD.

Difficulty in cognitive control among women with PMDD.

However, the performance of response inhibition among PMDD women is compatible to controls. This present study with adequate number of subjects demonstrated the deficit in performance of response inhibition in premenstrual phase among PMDD women. This result suggested that women with PMDD have impaired cognitive control specific in the premenstrual phase.

Besides, the premenstrual decline of cognitive control in PMDD womne is found only among those with GG genotype of HTR1A (rs6295). This resutl indicates that GG genotype of HTR1A (rs6295) are vulnerable to the mentrual effect on cognitive control among women with PMDD.

Conclusion

This study demonstrates the premenstrual decline of WM and cognitive control among women with PMDD. These deficits should be addressed when treating women with PMDD. Some tools providing assistance to short-term memory, such as screen note or event alarming, could be used to compensate their WM deficit in premenstrual phase. Counseling for inhibitory deficit could be provided to them to prevent negative results under poor cognitive control. The GG genotype of HTR1A (rs6295) associated with poorer premenstrual WM. Further, GG genotype of HTR1A (rs6295) determine the vulnerability to the menstrual effect and PMDD effect on cognitive function. How the GG genotype of HTR1A(rs6295) contribute the vulnerability of cognitive function to the menstrual or PMDD effect should be further evaluated in future. It would provide a insight to serotonin mechanism of PMDD.

III. 症狀學研究: Depression, irritability, and anxiety in women with Premenstrual dysphoric disorder (以接受刊登於 international journal of medical psychiatry)

Results: The PMDD group has higher scores in CESD, BDHIC-SF, and PSWQ in both the premenstrual and follicular phases. Paired *t-tests* demonstrated that the score of CESD, BDHIC-SF, and PSWQ was higher in the premenstrual phase than in the follicular phase among the PMDD group, but not in the control group. The two-way ANOVA in Table 2 and figure 1 demonstrated that there are significant premenstrual effects on the score of CESD, BDHIC-SF, and PSWQ. There is a significant interaction between the premenstrual effect and the PMDD effect on the score of CESD, BDHIC-SF, and PSWQ. It means that PMDD women had a higher premenstrual exacerbation effect on depression, hostility, and anxiety than the control group. The between-group analysis demonstrated that PMDD women had higher scores in CESD, BDHIC-SF, and PSWQ across the menstrual cycle.

The logistic regression in Table 3 demonstrated that the CESD score has a stronger effect on PMDD diagnosis. It indicates that depression is the most significantly associated factor of PMDD diagnosis. In this logistic regression model, the scores of PSWQ and BDHIC-SF were excluded when depression entered the regression model. The ROC curve analysis demonstrated the diagnostic accuracy (the area under ROC curve) of CIAS, BDHIC-SF, and PSWQ as 91.5%, 83.1%, and 79.5%.

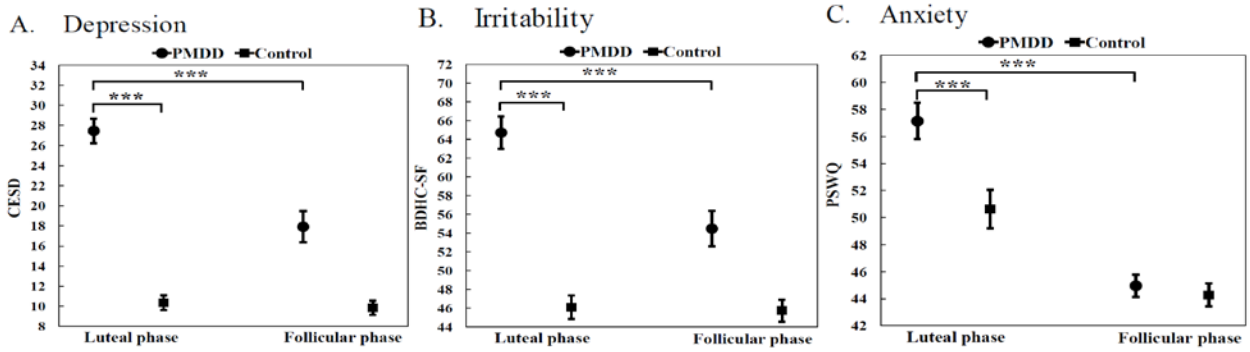


Table 1 The depression, anxiety, and irritability among PMDD and control group

Variables	PMDD group (Mean ± SD)	Paired t-test	Control group (Mean ± SD)	Paired t-test	Independent *t*-test
CESD					
Luteal	27.28 ± 9.71	6.362***	10.86 ± 7.64	1.215	-11.897***
Follicular	18.42 ± 12.60		10.01 ± 6.19		-5.407***
PSWQ					
Luteal	56.27 ± 10.67	5.525***	45.28 ± 7.62	1.122	-7.522***
Follicular	50.77 ± 11.79		44.63 ± 8.06		-3.861***
BEHIC-SF					
Luteal	64.17 ± 14.26	6.000***	46.59 ± 11.58	0.721	-8.563***
Follicular	55.05 ± 14.96		45.89 ± 10.09		-4.555***

CESD: Center for Epidemiological Studies' Depression Scale; PAWQ: Penn state worry questionnaire; BDHIC-SF: Buss-Durkee Hostility Inventory- Chinese Version- Short Form; ***: $p<0.001$

Table 2 The two factors repeated measures ANOVA for the premenstrual and PMDD effect on depression, anxiety, and hostility.

	With-subject analysis					
	df	Mean square	F	η^2		df
CESD						
MC	1	1865.463	36.784***	0.190	Intercept	1
MC*PMDD	1	1273.765	25.116***	0.138	PMDD	1
BDHIC-SF						
MC	1	1912.042	28.515***	0.154	Intercept	1
MC*PMDD	1	1407.375	20.989***	0.118	PMDD	1
PAWQ						
MC	1	747.514	27.248***	0.148	Intercept	1
MC*PMDD	1	466.457	17.003***	0.098	PMDD	1

CESD: Center for Epidemiological Studies' Depression Scale; PAWQ: Penn state worry questionnaire; BDHIC-SF: Buss-Durkee Hostility Inventory- Chinese Version- Short Form; ***: $p<0.001$

Table 3 The forward logistic regression model for diagnosis of PMDD among all subjects and linear regression model for symptoms severity and functional impairment of PMDD among women with PMDD in premenstrual phase.

Logistic regress (All subjects)			
For PMDD diangosis	**Wald**	**Exp(β)**	**50% CI**
Age (yr)	0.004	1.01	0.86-1.18
Education level (yr)	0.412	0.89	0.62-1.28
CESD	43.73***	1.23	1.15-1.31
Linear regression (Women with PMDD)			

For symptoms severity	t	β
Age (yr)	0.14	-0.03
Education level (yr)	1.21	-0.62
CESD	3.85***	0.27
For Functional impairment	**t**	**β**
Age (yr)	1.51	0.17
Education level (yr)	1.71	0.42
BDHIC-SF	3.40**	0.08

CESD: Center for Epidemiological Studies' Depression Scale; BDHIC-SF: Buss-Durkee Hostility Inventory-Chinese Version- Short Form; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$

Discussion

As the criteria of PMDD in DMS 5, our result support that depression, anxiety, and irritability were all higher among women with PMDD than those among control group. This result demonstrated that women with PMDD experience higher multiple dimension symptoms in the premenstrual phase. In line with previous review(Landen & Eriksson, 2003), this result also support that PMDD is not a variant of depressive or anxiety disorder which consisted of only one dimension of symptoms. This result might suggest PMDD is a distinct disorder with multiple dimensions of symptoms. Further, women with PMDD would experience their symptoms for more than 3000 days in their life(Rapkin & Winer, 2009).

Further, our results demonstrate the depression, anxiety, and irritability become more severe in premenstrual phase among women with PMDD, but not in control group. Previous results have suggest the premenstrual exacerbation of depression or other symptoms among women with PMDD(Hsiao, Hsiao, & Liu, 2004; Miyaoka et al., 2011). However, those result was based retrospective investigation. These presenting results based on prospective investigation support that the premenstrual exacerbation of depression, anxiety, and irritability among women with PMDD. This result might suggest these symptoms yield to the endocrine or neurobiological effect of menstrual cycle in women with PMDD.

Our result demonstrate women with PMDD had higher depression, anxiety, and irritability then control group not only in premenstrual phase, but also in follicular phase. Although the severity of these four symptoms are decreased significantly in follicular phase in comparison to premenstrual phase, their severe is still higher than control group. Although the criteria of PMDD in DSM 5 has suggest that its symptoms will become *minimal* or absent in the week post-menses, our study proved that the symptoms would become minimal, but not absent, in follicular phase. Thus, women with PMDD does not totally remit in follicular phase. This results might suggest that there must be factors other than menstrual-cycle related factors contributing to psychopathology of PMDD in follicular phase.

Previous review has suggest that irritability is a more prominent symptoms based on its higher severity or prevalence among PMDD women(Angst, Sellaro, Merikangas, & Endicott, 2001; Landen & Eriksson, 2003). However, higher severity or prevalence could not conclude its importance because it might also prevalent in control group. In these study, we determine the most pathognomonic symptoms by logistic regression and ROC analysis. Although depression, anxiety, and irritability were all associated with PMDD, depression is the only variable to enter the regression model for PMDD. The association between anxiety, irritability, and PMDD become insignificant when depression enter the regression model. It means depression is the most proximally associated symptoms of PMDD diagnosis among these three cardinal symptoms.

Further, depression has the highest diagnostic accuracy(91.5%) among this three symptoms. It indicates that higher depression contributes to diagnosis of PMDD more than anxiety or irritability. This result might suggest that depression is the most pathognomonic symptom of PMDD among these three symptoms. Further, depression is the most significant associate factor of severity of PMDD among women with PMDD. These results all suggest PMDD could be represented mostly by depression.

Conclusion

The presenting studies demonstrate the premenstrual exacerbation of depression, anxiety, and irritable among women with PMDD, but not in those without PMDD. The depression is the most associated symptoms of PMDD and represent the severity of PMDD. The irritability contribute to functional impairment of PMDD. These results suggest depression and irritability are two cardinal symptoms of PMDD. Further, the trend for association between LH and anxiety or irritability might indicate the possible role of LH in mechanism of PMDD.

IV. 行為反應研究: Behavior inhibition and behavior approach system in PMDD women and their hormone correlates. (本研究已投稿 psychiatry and clinical neuroscience)

Results:There is no significant difference in age or educational level between PMDD and the control group in table 1. The PMDD group has higher scores in reward responsiveness, drive, fun seeking, BAS in both the premenstrual and follicular phases. Besides the scores of BIS were higher among PMDD group in premenstrual phase, but not in follicular phase. Paired *t-test* demonstrated that the score of BIS was higher in the premenstrual phase than that in the follicular phase among the PMDD group, but not in the control group. However, there is no difference between BAS in premenstrual and follicular phase.

The repeated measure two-way ANOVA in table 2 demonstrated that there is a significant interaction between the premenstrual effect and the PMDD effect over the score of BIS. It means that PMDD women had a higher premenstrual exacerbation effect on behavior inhibition than the control group. The between group analysis demonstrated that PMDD women had higher scores in BIS/BAS across the menstrual cycle.

The logistic regression in table 3 demonstrates that score of BAS enter the model for PMDD diagnosis followed by BIS. It indicates that BAS is more associated with PMDD diagnosis than BAS. The correlation analysis in women with PMDD (Figure 1) reveal that progesterone significantly negatively correlates with fun seeking(r=-0.33, p=0.002) and total score of BAS (r=-0.25, p=0.024). The change of progesterone from follicular phase to premenstrual phase was also associated with premenstrual change of fun seeking(r=-0.35, p=0.001), BAS (r=-0.33, p=0.003), and reward drive (-0.26, p=0.019). However, the associations were not significant among control group. Further, BIS correlates with depression, anxiety, and irritability and BAS correlates with impulsivity and food craving in premenstrual phase among women with PMDD(Table 4).

Table 1 The demographic data, behavior inhibition system (BIS), and behavior approach system (BAS) in both premenstrual and follicular phases among women with premenstrual dysphoric disorder (PMDD) and controls.

Variables	PMDD group (Mean ± SD) N = 83	Paired t-test	Control group (Mean ± SD) N = 76	Paired t-test	Independent *t*-test
Education level (yr)	16.12 ± 1.16		16.27 ± 1.73		-0.587
Age (yr)	23.46 ± 3.21		23.60 ± 3.49		-0.243

BIS					
Premenstrual	21.75 ± 2.25	3.827***	20.11 ± 2.58	0.705	4.016***
Follicular	20.58 ± 2.82		19.95 ± 2.70		1.370
Reward					
Premenstrual	18.03 ±2.01	-0.299	16.80 ± 1.97	-0.290	3.685***
Follicular	18.12 ± 2.27		16.85 ± 1.96		3.572***
Drive					
Premenstrual	13.00 ± 2.17	-0.054	12.17 ± 1.84	0.666	2.435*
Follicular	13.01 ± 2.56		12.04 ± 1.70		2.641**
Fun					
Premenstrual	11.81 ± 2.34	-0.437	10.61 ± 2.02	-0.172	3.262**
Follicular	11.91 ± 2.27		10.64 ± 1.87		3.654***
BAS					
Premenstrual	42.84 ± 4.87	-0.326	39.59 ± 4.51	0.138	4.125***
Follicular	43.04 ± 5.67		39.53 ± 4.29		4.186***
Progesterone			N=75		
Premenstrual	9.66 ±8.87	8.162***	9.14 ±8.55	7.768***	0.351
Follicular	0.84 ±1.24		1.09 ±1.88		-0.920

Reward: BAS Reward responsiveness; Drive: BAS drive; Fun: BAS fun seeking;
**: $p<0.01$; ***: $p<0.001$

Table 2 The repeated measure two-way ANOVA for the effect of premenstrual dysphoric disorder (PMDD) diagnosis and premenstrual phase on score of behavior inhibition system (BIS) and behavior approach system (BAS).

		With-subject analysis			
	df	**Mean square**	**F**	**η^2**	
BIS					
MC	1	31.03	12.494**	0.082	Intercept
MC*PMDD	1	17.84	7.185**	0.049	PMDD
BAS					
MC	1	0.43	0.045	0.000	Intercept
MC*PMDD	1	1.522	0.129	0.001	PMDD

MC: menstrual cycle effect;
*: $p<0.05$; **: $p<0.01$; ***: $p<0.001$

Table 3 The forward logistic regression model for diagnosis of premenstrual dysphoric disorder (PMDD) among all subjects.

Logistic regress	**All subjects**		
For PMDD diagnosis	**Wald**	**Exp(β)**	**95% CI**
Age (yr)	0.58	1.05	0.93-1.20

Education level (yr)	2.74	0.77	0.57-1.05
Behavior activation	11.76**	1.35	1.07-1.25
Behavior inhibition	12.80***	1.16	1.14-1.60

**: $p<0.01$; ***: $p<0.0$

Discussion

This is the first study to focus on the sensitivity to reinforcement of women wtih PMDD. It demonstrates the difference on BIS and BAS system of PMDD women without pharmacological treatment by using prospective investigation. This result suggests that women with PMDD have higher reward sensitivityboth in premenstrual and follicular phase. It indicates the difference on reward sensitivity is stable across the menstrual cycle. It supports that the reward sensitivity of women with PMDD is different from normal population not only in premenstrual phase, but also in luteal phase. Further, the BAS score did not change by menstrual cycle in both women with PMDD or controls. Thus, higher reward sensitivity representes a fundamental characteristics of PMDD which is not vulnerable to menstrual cycle. Besides, the logistic regression analysis demonstrated that BAS entered the model for PMDD, followed by BIS. This result suggests reward sensitivity was more associated with PMDD than aversion sensitivity. It suggests that increased rewarding sensitivity is an important dimension of psychopathology in PMDD that has not been well evaluated.

The most important finding in this study is that progesterone is negatively associated with BAS and fun seeking score. Previous reports has demonstrated that the progesterone decrease the reaction to reward(Sakaki & Mather, 2012). Our result in women with PMDD demonstrated those had higher progesterone level had lower reward sensitivity, particular fun-seeking. Thus, this result might suggest that the progesterone has played a role, as a between-subjects factor, in determining the sensitive to reward among women with PMDD.

In line with our previous report(Yen et al., 2011), women with PMDD have higher BIS, representing sensitive to aversive stimuli, than control group. Further, our results demonstrate the BIS become higher in premenstrual phase among women with PMDD, but not in control group. Although the sensitivity to aversive stimuli has been defined as a fundamental characters(Corr, 2004), these presenting results support that the premenstrual exacerbation of aversion sensitivity among women with PMDD. Since the menstrual cycle effect on aversion sensitivty is insignificant among control group, the pathology of premenstrual exacerbation was not simply the menstrual cycle effect on these symptoms, but the higher vulnerability of women with PMDD to the effect menstrual cycle on BIS. This claim based on our result is inline previous hypothesis that PMDD has a different response to normal hormone level (Poiana et al., 2009).

Conclusion: The presenting studies demonstrate higher reward sensitivity of women with PMDD across menstrual cycle and its contribution to food craving and impulsivity. Progesterone level and its change across menstrual cycle negatively contribute to the reward sensitivity of women with PMDD, but not to that of controls. It supports the reward sensitivity of women with PMDD was more vulnerable to progesterone effect than controls. We also reveal that the prementraul exacerbation of sensitivity to aversion and its contribution to depression, anxiety, and hostility among women with PMDD. These results supports that reward or aversion sensitivyt play an important role in mechanism of PMDD and deserve detail studies.

V. 功能性磁振造影研究: The brain activation of food craving in premenstrual phase of women with PMDD and controls

Results: A total of 20 females with PMDD and 20 controls were recruited in the analysis for fMRI data. They are arranged to see the sweet food picture under investigation of fMRI.

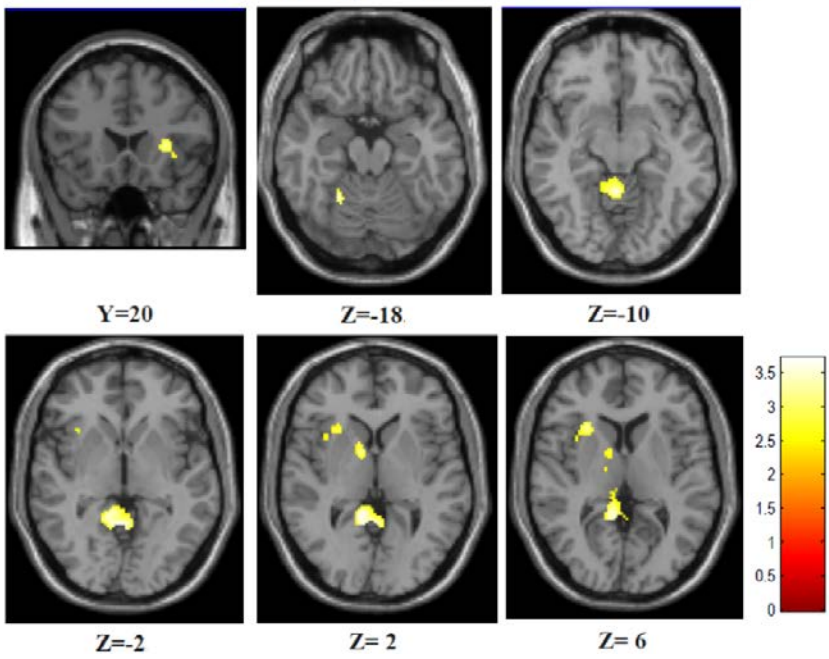
Cue-induced craving paradigm in fMRI scanning: The cues used to induce food cravings to 70 sweet food picture. The 70 neutral pictures were the pictures selected from International affective picture system. Each subject then viewed the 140 images in a pseudo-random sequence while wearing the fMRI display goggles. Each image was shown for 2 seconds, and the intervals between images were randomly jittered so that they ranged from 3.2 seconds to 8.3 seconds. The paradigm was run for 800 seconds after 5 dummy scans (10s). The final analysis included 400 volumes of data (excluding dummy scans).

All time series data of blood-oxygen-level-dependent(BOLD) contrast were exported from the GE system and converted into statistical parametric mapping (SPM 5) format using MRIcro. The subsequent image preprocessing and statistical analysis was performed using SPM5 package (Wellcome Department of Cognitive Neurology, London, UK). Each image was realigned for motion correction, and the structural image was co-registered to the mean motion-corrected functional image for each participant. The realigned datasets were normalized to Montreal Neurological Institute (MNI) space. An 8-mm, full-width, half-maximum Gaussian kernel was used for data smoothing.

The analysis was conducted by using an SPM5 to model sweet food cues versus neutral stimulation as explanatory variables within the context of a general linear model on a voxel-by-voxel basis. A random effects model was used to combine the gaming and smoking cue reactivity of individual subjects into a group analysis with comparison t test. After including the contrast for sweet food cue [sweet food cue -neutral cue] reactivates in each group. The brain activation for food craving in each group with a threshold of $p<0.05$, a corrected false discovery rate (FDR), and a cluster size > 20 voxels. The group effect for gaming or smoking cue reactivity was determined with a $p<0.005$ threshold in voxel level.

The comparison analysis demonstrated that the PMDD group have higher brain activation over hippocampus, posterior cingulate, precuneus, inferior frontal lobe/insula, and superior frontal lobe. This result suggest that PMDD women have higher brain reaction to sweet food picture.

The brain activation of sweet food craving higher among PMDD group than that of control group. (P<0.005 in voxel level)



Discussion

The result support that the sweet food picture drive a higher sweet food craving response over hippocampus, inferior frontal lobe/insula, posterior cingulate, precuneus, and superior frontal lobe. The hippocampus play an essential role in the emotional memory. Precuenus participate in the visual processing, the insula associated with interceptive sensation, superior frontal lobe is associated with craving response. Our result support that food cue would provoke a stronger brain reaction among women with PMDD than those among controls. Further, there brain areas had been reported to associated with craving response. Thus, our result might dmoentrate the mechanism to explain the increased appetite to sweet food among women with PMDD.

VI. 功能性磁振造影研究: The brain activation for low and higher demanding working memory among women with PMDD.

Results: A total of 20 females with PMDD and 20 controls were recruited in the analysis for fMRI data. They are arranged to complete the 2 back and 3 back task under investigation of fMRI.

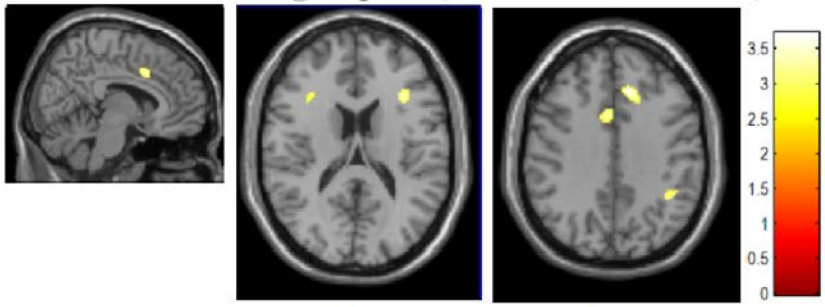
2 back and 3 back task: A variant N-back paradigm modified from Braver's study was utilized to assess the phonological and visual-spatial working memory (Figure 1 in supplement of material, SOM1). In the 0-back condition of the first section, subjects responded to a single pre-specified target letter (e.g., ''6''). In the 2-back and 3-back conditions, the target was any number that was identical to the one presented two or three trials back, respectively. Thus, WM load increased incrementally from the 0-back to the 3-back condition. Stimuli included the numbers 1 to 6 presented as pseudorandom sequences; presented centrally (200-ms duration, 800-ms interstimulus interval). All participants were asked to read all shown numbers in mind to help them remember and trigger the phonological loop. Subjects responded to each stimulus with their dominant hand, pressing the left button with the right thumb for targets (7 in 30 trials). Conditions were run in blocks of 30s (30 stimuli) and arranged as 0-2-3-2-0-3-2-3-0.

All time series data of blood-oxygen-level-dependent(BOLD) contrast were exported from the GE system and converted into statistical parametric mapping (SPM 5) format using MRIcro. The subsequent image preprocessing and statistical analysis was performed using SPM5 package (Wellcome Department of Cognitive Neurology, London, UK). Each image was realigned for motion correction, and the structural image was co-registered to the mean motion-corrected functional image for each participant. The realigned datasets were normalized to Montreal Neurological Institute (MNI) space. An 8-mm, full-width, half-maximum Gaussian kernel was used for data smoothing.

First, two mean images of subtraction for each subject were created: the contrast of N0 block subtracted from N2 block and that of N2 block subtracted from N3 in both phonological and visual-spatial working memory tasks on a voxel-by-voxel basis with SPM8. The subtraction demonstrated that the brain activation associated with low demands and the increased load of working memory. Then, these mean images were combined in a full-factor analysis. One independent factor, PMDD group versus control group, and one dependent factor. The activation responses for the low level working memory (N2-N0) or increased load of working memory (N3-N2) were demonstrated for phonological working memory among each group.

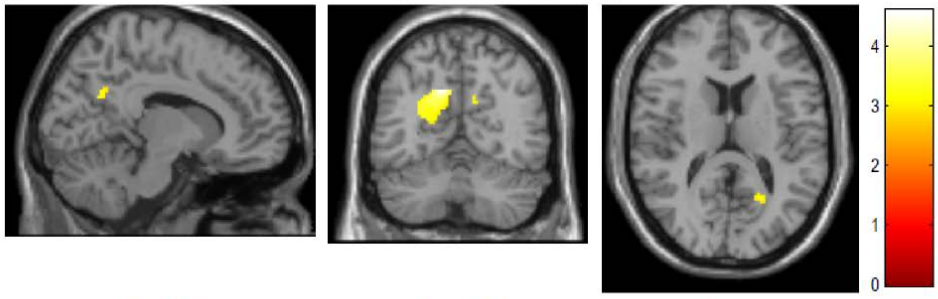
The comparison analysis demonstrated that women with PMDD have a lower brain activation over superior frontal lobe than control group when processing working memory. On the other hand, women with PMDD have a lower brain activation over posterior cingulate/precuneus in premenstrual phase than follicular phase when processing working memory.

The brain activation of working memory higher among control group than that of PMDD group. (P<0.005 in voxel level)



X=8 Z=18 Z=36

The brain activation of working loading higher among follicular phase than that of premenstrual phase among PMDD group. (P<0.005 in voxel level)



X=12 Y=-62 Z=14

Discussion

This result supported that PMDD women have an impaired working memory function over superior frontal lobe in the premenstrual phase in comparison to control group. This result demonstrated the possible mechanism to explain the impaired working memory function in our previous study. On the other hand, it also demonstrated that women with PMDD have impaired brain activation over precuneus and posterior cingulate. These results might suggest there is a difference brain activation of working memory between premenstrual phase and follicular phase among women with PMDD. These results might indicate that women with PMDD have a impaired brain activation in premenstrual phase. However, the between group difference and between phase difference are over the difference brain areas.

Reference List

Albert, P. R. (2012). Transcriptional regulation of the 5-HT1A receptor: implications for mental illness. *Philos Trans R Soc Lond B Biol Sci, 367*(1601), 2402-2415. doi: 10.1098/rstb.2011.0376
rstb.2011.0376 [pii]

Albert, P. R., Le Francois, B., & Millar, A. M. (2011). Transcriptional dysregulation of 5-HT1A autoreceptors in mental illness. *Mol Brain, 4*, 21. doi: 10.1186/1756-6606-4-21
1756-6606-4-21 [pii]

Amin, Z., Canli, T., & Epperson, C. N. (2005). Effect of estrogen-serotonin interactions on mood and cognition. *Behav Cogn Neurosci Rev, 4*(1), 43-58. doi: 4/1/43 [pii]
10.1177/1534582305277152

Angst, J., Sellaro, R., Merikangas, K. R., & Endicott, J. (2001). The epidemiology of perimenstrual

psychological symptoms. *Acta Psychiatr Scand, 104*(2), 110-116. doi: acp412 [pii]

Association., American Psychiatric (Ed.). (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)*. Arlington: Am erican Psychiatric Association.

Born, L., Koren, G., Lin, E., & Steiner, M. (2008). A new, female-specific irritability rating scale. *J Psychiatry Neurosci, 33*(4), 344-354.

Corr, P. J. (2004). Reinforcement sensitivity theory and personality. *Neurosci Biobehav Rev, 28*(3), 317-332. doi: 10.1016/j.neubiorev.2004.01.005

S014976340400034X [pii]

Dhingra, V., Magnay, J. L., O'Brien, P. M., Chapman, G., Fryer, A. A., & Ismail, K. M. (2007). Serotonin receptor 1A C(-1019)G polymorphism associated with premenstrual dysphoric disorder. *Obstet Gynecol, 110*(4), 788-792. doi: 110/4/788 [pii]

10.1097/01.AOG.0000284448.73490.ac

Drago, A., Ronchi, D. D., & Serretti, A. (2008). 5-HT1A gene variants and psychiatric disorders: a review of current literature and selection of SNPs for future studies. *Int J Neuropsychopharmacol, 11*(5), 701-721. doi: S1461145707008218 [pii]

10.1017/S1461145707008218

Estrada-Camarena, E., Lopez-Rubalcava, C., & Fernandez-Guasti, A. (2006). Facilitating antidepressant-like actions of estrogens are mediated by 5-HT1A and estrogen receptors in the rat forced swimming test. *Psychoneuroendocrinology, 31*(8), 905-914. doi: S0306-4530(06)00087-4 [pii]

10.1016/j.psyneuen.2006.05.001

Halbreich, U. (2003). The etiology, biology, and evolving pathology of premenstrual syndromes. *Psychoneuroendocrinology, 28 Suppl 3*, 55-99. doi: S0306453003000970 [pii]

Hartlage, S. A., Arduino, K. E., & Gehlert, S. (2001). Premenstrual dysphoric disorder and risk for major depressive disorder: a preliminary study. *J Clin Psychol, 57*(12), 1571-1578. doi: 10.1002/jclp.1119 [pii]

Hsiao, M. C., Hsiao, C. C., & Liu, C. Y. (2004). Premenstrual symptoms and premenstrual exacerbation in patients with psychiatric disorders. *Psychiatry Clin Neurosci, 58*(2), 186-190. doi: 1215 [pii]

Huo, L., Straub, R. E., Roca, C., Schmidt, P. J., Shi, K., Vakkalanka, R., . . . Rubinow, D. R. (2007). Risk for premenstrual dysphoric disorder is associated with genetic variation in ESR1, the estrogen receptor alpha gene. *Biol Psychiatry, 62*(8), 925-933. doi: S0006-3223(06)01558-7 [pii]

10.1016/j.biopsych.2006.12.019

Koldzic-Zivanovic, N., Seitz, P. K., Watson, C. S., Cunningham, K. A., & Thomas, M. L. (2004). Intracellular signaling involved in estrogen regulation of serotonin reuptake. *Mol Cell Endocrinol, 226*(1-2), 33-42. doi: S0303-7207(04)00295-3 [pii]

10.1016/j.mce.2004.07.017

Landen, M., & Eriksson, E. (2003). How does premenstrual dysphoric disorder relate to depression and anxiety disorders? *Depress Anxiety, 17*(3), 122-129. doi: 10.1002/da.10089

Landen, M., Erlandsson, H., Bengtsson, F., Andersch, B., & Eriksson, E. (2009). Short onset of action of a serotonin reuptake inhibitor when used to reduce premenstrual irritability. *Neuropsychopharmacology, 34*(3), 585-592. doi: 10.1038/npp.2008.86

npp200886 [pii]

Lokuge, S., Frey, B. N., Foster, J. A., Soares, C. N., & Steiner, M. (2011). Depression in women: windows of vulnerability and new insights into the link between estrogen and serotonin. *J Clin Psychiatry, 72*(11), e1563-1569. doi: 10.4088/JCP.11com07089

Miyaoka, Y., Akimoto, Y., Ueda, K., Ujiie, Y., Kametani, M., Uchiide, Y., & Kamo, T. (2011). Fulfillment of the premenstrual dysphoric disorder criteria confirmed using a self-rating questionnaire among Japanese women with depressive disorders. *Biopsychosoc Med, 5*, 5. doi: 1751-0759-5-5 [pii]
10.1186/1751-0759-5-5

Moses-Kolko, E. L., Berga, S. L., Greer, P. J., Smith, G., Cidis Meltzer, C., & Drevets, W. C. (2003). Widespread increases of cortical serotonin type 2A receptor availability after hormone therapy in euthymic postmenopausal women. *Fertil Steril, 80*(3), 554-559.

Poiana, C., Musat, M., Carsote, M., & Chirita, C. (2009). Premenstrual dysphoric disorder: neuroendocrine interferences. *Rev Med Chir Soc Med Nat Iasi, 113*(4), 996-1000.

Rapkin, A. J., & Akopians, A. L. (2012). Pathophysiology of premenstrual syndrome and premenstrual dysphoric disorder. *Menopause Int, 18*(2), 52-59. doi: 10.1258/mi.2012.012014
18/2/52 [pii]

Rapkin, A. J., & Winer, S. A. (2009). Premenstrual syndrome and premenstrual dysphoric disorder: quality of life and burden of illness. *Expert Rev Pharmacoecon Outcomes Res, 9*(2), 157-170. doi: 10.1586/erp.09.14

Rasgon, N. L., Altshuler, L. L., Fairbanks, L. A., Dunkin, J. J., Davtyan, C., Elman, S., & Rapkin, A. J. (2002). Estrogen replacement therapy in the treatment of major depressive disorder in perimenopausal women. *J Clin Psychiatry, 63 Suppl 7*, 45-48.

Ryan, J., Scali, J., Carriere, I., Peres, K., Rouaud, O., Scarabin, P. Y., . . . Ancelin, M. L. (2012). Estrogen receptor alpha gene variants and major depressive episodes. *J Affect Disord, 136*(3), 1222-1226. doi: 10.1016/j.jad.2011.10.010
S0165-0327(11)00654-9 [pii]

Sakaki, M., & Mather, M. (2012). How reward and emotional stimuli induce different reactions across the menstrual cycle. *Soc Personal Psychol Compass, 6*(1), 1-17. doi: 10.1111/j.1751-9004.2011.00415.x

Schneider, L. S., Small, G. W., & Clary, C. M. (2001). Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. *Am J Geriatr Psychiatry, 9*(4), 393-399.

Steiner, M., & Pearlstein, T. (2000). Premenstrual dysphoria and the serotonin system: pathophysiology and treatment. *J Clin Psychiatry, 61 Suppl 12*, 17-21.

Sundermann, E. E., Maki, P. M., & Bishop, J. R. (2010). A review of estrogen receptor alpha gene (ESR1) polymorphisms, mood, and cognition. *Menopause, 17*(4), 874-886. doi: 10.1097/gme.0b013e3181df4a19
00042192-201017040-00033 [pii]

Yen, J. Y., Chen, C. C., Chang, S. J., Ko, C. H., Chen, C. S., & Yen, C. F. (2011). Hostility, impulsivity, and behavior inhibition among women with PMDD. *CNS Spectr*. doi: Yen [pii]

國科會補助計畫衍生研發成果推廣資料表

日期:2013/10/24

國科會補助計畫	計畫名稱: 經前不悅症之基因多型性、生理因子、腦影像學與精神病理學研究(重點代號: GM07)
	計畫主持人: 柯志鴻
	計畫編號: 100-2629-B-037-001-MY2　　學門領域: 性別主流科技計畫

無研發成果推廣資料

100 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：100-2629-B-037-001-MY2
計畫名稱：經前不悅症之基因多型性、生理因子、腦影像學與精神病理學研究(重點代號:GM07)	

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	0	0	100%		
		研討會論文	0	0	100%		
		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	1	100%		
國外	論文著作	期刊論文	2	2	100%	篇	目前已接受刊登 2 篇: (1)The effect of serotonin 1A receptor polymorphism on the cognitive function of Premenstrual Dysphoric Disorder（已接受刊登於 European Achieve of Psychiatry and clinical neuroscience in

							刊登於International Journal of Medical Psychiatry, in press)
		研究報告/技術報告	0	0	100%		
		研討會論文	0	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（外國籍）	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	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。)	本研究上有相關論文投稿中: 1.完成第一次 revised 審核中(1 篇) (1)The association between Premenstrual Dysphoric Disorder and Internet Use Disorder. (submitting to Women & health, first revised and under review) 2.已投稿審核中(2 篇) (1)The Interaction between Polymorphism of Serotonin 1A Receptor and Estrogen Receptor α Predicts Premenstrual Dysphoric Disorder (submitting to hormone and behavior under reviewing) (2)Progesterone and Reinforcement Sensitivity systems in PMDD women (submitting to psychiatry and clinical neuroscience, under review) 3.撰寫中(3 篇) (1)The brain correlates of sweet food craving among women with PMDD. (2)The brain correlates of working memory among women with PMDD: the effect of menstrual cycle. (3)The sweet food craving of women with PMDD: menstrual cycle, hormone, and serotonin 1A receptor polymorphism.					

	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	

國科會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)

本研究目前已接受刊登 2 篇:

1.The effect of serotonin 1A receptor polymorphism on the cognitive function of Premenstrual Dysphoric Disorder（已接受刊登於 European Achieve of Psychiatry and clinical neuroscience, in press）

2.Depression, irritability, and anxiety in women with Premenstrual dysphoric disorder（已接受刊登於 International Journal of Medical Psychiatry, in press）

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)

一、本研究以追蹤兩個月完成個案之診斷確認，是少數依據嚴格條件進行之臨床研究。同時在追蹤期間，發現經前不悅症症狀變化的主要時間在排卵期到月經前一週，亦即其症狀從無到有是在黃體期中出現，此結果顯示，若要討論經前不悅症之荷爾蒙之影響，未來研究應觀察排卵期到經前的變化，而非比較黃體期或濾泡期。

二、本研究在嚴格的個案篩選下，發現 Serotonin 1A Receptor and Estrogen Receptor α Genes 之基因多型性與經前不悅症有顯著相關，結果顯示在帶有 G allel of ESR1-XbaI 的個案中，GG genotype of serotonin IA receptor 之個案有 4.8 倍罹患機前不悅症之風險。此結果驗證，經前不悅症同時受到血清素及女性荷爾蒙相關基因多型性之影響。

三、本研究經前不悅症患者於經前有認知功能缺損(工作記憶與反應抑制)之表現，此表現不僅表現在與對照組之差異，亦表現在經前與濾泡期之差異。此結果顯示，經前不悅症婦女之認知缺陷的確受到月經週期之影響，除此之外，亦驗證上述兩基因之交互作用顯著影響基因缺陷。呈現認知缺陷可能之生理機轉。

四、本研究再次驗證經前不悅症婦女於經前有較高的食物渴求傾向，且此傾向與情緒及衝

動控制有關。進一步功能性磁振造影研究則顯示於食物圖片的刺激下，經前不悅症個案於 hippocampus, inferior frontal lobe/insula, posterior cingulate, precuneus, and superior frontal lobe 有較高之活性。這些研究結果顯示，經前不悅症個案經前之食慾增加可能是食物渴求之表現，同時此表現與前腦、腦島、及海馬迴等渴求相關區域有關。為第一個針對經前不悅症婦女的食物渴求進行之功能性磁振造影研究。

五、此研究成功整合精神病理、影像醫學、基因多型性、及女性荷爾蒙之研究。由其在分析過程中，利用不同層面的結果，進行交互作用分析，藉以基因多型性與荷爾蒙，如何經由對腦功能及認知功能之影響，而促成經前不悅症之症狀，已呈現較為完整之機轉，提供未來研究做為有效的研究模式。