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注意力不足過動症之神經生物學與基因學研究

Neurobiological and Genetic Studies on Attention Deficit

Hyperactivity Disorder

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國立臺灣大學博士學位論文
口試委員會審定書

注意力不足過動症之神經生物學與基因學研究

Neurobiological and Genetic Studies on Attention Deficit Hyperactivity Disorder

本論文係商志雍君（D96421005）在國立臺灣大學臨床醫學研究所完成之博士學位論文，於民國 102 年 1 月 7 日承下列考試委員審查通過及口試及格，特此證明

口試委員：

_（簽名）_

（指導教授）

系主任、所長 _____ （簽名）

誌謝

回首這五年多的博士班歷程，在高淑芬教授的指導之下，我從一個學術研究的門外漢，到成為一個神經生物研究的學習者，這中間要感謝太多的人，其中首先要感謝的當然是我的恩師高淑芬教授，她總是將學生們的需要放在第一優先，高教授非常有耐心地教導我在研究領域上的學習，特別是在神經生物學、藥物學、以及基因遺傳學等方面，我從高教授的帶領上獲得難以言喻的幫助。同時高教授也以身作則，在從事學術研究與照顧家庭生活兩方面都成為我們的最佳模範。另外也要感謝楊偉勛教授、曾文毅教授、陳為堅教授、陳嘉祥教授、邱麗珠教授、以及藍先元教授在博士論文上給學生的寶貴意見，讓我對於注意力不足過動症的研究有了更廣闊與完整的視野，未來也期許自己將博士班的畢業當作一個起點，對於注意力不足過動症的病理生理學機轉能有更深入的探討。

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為祂不但賜福給祂的兒女們，更是讓祂的兒女們成為別人的祝福！

目錄

中文摘要

關鍵詞：注意力不足過動症，劍橋神經心理測驗，執行功能，視覺記憶，額葉紋狀體神經路徑，擴散頻譜造影，多巴胺轉運基因，單套體，連鎖不平衡

注意力不足過動症常合併執行功能障礙，但其他認知功能障礙則較少被研究，另外也沒有研究證實 atomoxetine 藥物治療可以改善這些認知功能障礙，而這些認知功能障礙潛在的神經構造與基因病因仍未有定論。本博士論文將分成以下四個層面來回答上述問題。

（一）神經心理學方面：(a) 探索 53 位在兒童期被診斷為 ADHD 的青少年及 53 位配對的健康對照組的執行功能，以劍橋神經心理測驗 (Cambridge Neuropsychological Test Automated Battery，CANTAB) 測量其執行功能，結果發現 ADHD 患者在這四個執行功能測驗表現均較對照組差，證實 ADHD 青少年患者有顯著的執行功能障礙，並在面對複雜作業時需要額外協助。

(b) 以 279 位 ADHD 患者、其未發病手足 (n=108)、及 173 位健康對照組，探索其執行功能與視覺記憶是否可以成為神經心理學的內表現型。我們使用 CANTAB 來測量執行功能以及視覺記憶，結果發現 ADHD 患者和其未發病手足在四個執行功能與四個視覺記憶測驗表現較健康對照組差，未發病手足在兩個視覺記憶測驗的表現介於 ADHD 和對照組之間，證實執行功能和視覺記憶確實可作為 ADHD 的神經心理學內表現型。

（二）藥物學方面：以 30 位 8 到 16 歲未曾服用過藥物的 ADHD 患者，進行一項持續 12 週開放標籤的 atomoxetine 藥物試驗，以瞭解其執行功能及視覺記憶在用藥後 4 週和 12 週的改善，結果發現患者在服藥後除了臨床表現及社會功能有顯著進步，在所測試的四項執行功能和兩項視覺記憶表現均有明顯進步，顯示 atomoxetine 可有效改善 ADHD 患者的執行功能與視覺記憶障礙。

（三）神經影像學方面：以 25 位 ADHD 患童及 25 位在年齡、性別、慣用

手、以及智商配對的健康對照組，瞭解額葉紋狀體神經束的完整性以及其和執行功能的相關性。結果發現患者以擴散頻譜造影 (diffusion spectrum imaging，DSI) 重建的兩側各四條額葉紋狀體神經路徑 (背外側、內側、眼窩前額葉、及腹外側) 的一般性之部分異向性 (generalized fractional anisotropy) 值均較對照組低，且和 ADHD 的症狀嚴重度和執行功能障礙有顯著相關，特別是左側的眼窩前額葉和腹外側等神經纖維束。

（四）基因關聯性方面：(a) 以 273 位 ADHD 家族 (n=906) 的 DNA 在 DAT1 基因上找出 14 個單核苷酸多型性 (SNP) 與 3´variable number of tandem repeat (VNTR)，結果這 15 個基因標記的 LD 結構，包含 3 個單套體區間，第一個區間大小為 19kb，位於第二、四、六個內顯子，第二個區間大小為 3kb，位於第八、十一個內顯子，第三個區間大小為 953bp，位於 3´UTR。單套體分析發現 rs27048 (C) /rs429699 (T) 與注意力不足亞型有顯著相關，在量性分析上也發現 rs27048 (C) /rs429699 (T) 與注意力不足症狀的嚴重度有顯著相關，顯示 DAT1 基因在 ADHD 的注意力不足亞型的病理生理機轉上扮演重要角色。

(b) DAT1 基因與執行功能的關聯性：以 382 位 ADHD 家族 (n=1298) 的 DNA 樣本及其執行功能進行分析。單套體分析發現，第一個單套體區間 rs403636 (G) /rs463379 (C) /rs393795 (C) /rs37020 (G) 和空間工作記憶的錯誤量有顯著相關性。顯示 DAT1 基因在 ADHD 的空間工作記憶障礙扮演重要角色。

綜合以上研究，本博士研究發現 ADHD 除了有執行功能的障礙之外，同時是世界上第一個研究證實視覺記憶是內表現型，並且 atomoxetine 治療可以改善執行功能與視覺記憶障礙，而 ADHD 的執行功能障礙與額葉紋狀體神經聯結及 DAT1 基因變異有明顯相關性，未來需要藉由藥物基因學以及影像基因學的研究以建立 ADHD 的病理生理機轉。

英文摘要

Keywords and Abbreviations: Attention-deficit/hyperactivity disorder (ADHD), frontostriatal tracts (FS), diffusion spectrum imaging (DSI), executive function (EF), visual memory (VM), Cambridge Neuropsychological Test Automated Battery (CANTAB), DAT1, haplotype, linkage disequilibrium (LD)

Although ADHD is often associated with executive deficits, little research has report other cognitive dysfunction in ADHD. No study has investigated the effect of atomoxetine on the cognitive dysfunction in children with ADHD. In addition, the neural correlates and genetic variants of cognitive dysfunction is still inconclusive. The doctoral thesis will answer these questions from four approaches.

(1) Neuropsychological approach: (a) Using 53 adolescents with childhood diagnosis of ADHD, and 53 matched controls, we examined their EF assessed by using the tasks involving the EF of the CANTAB. The ADHD group performed worse in all the EF tasks, and needed extra assistance while complex tasks were assigned.

(b) Using 279 adolescents with ADHD, 108 unaffected siblings and 173 controls, we examined their EF and VM to test whether EF and VM can be potential endophenotypes for ADHD. The ADHD probands and the unaffected siblings significantly performed worse in all the EF tasks. The unaffected siblings occupied an intermediate position between ADHD probands and controls in the performance on two VM tasks, suggesting that EF and VM can be useful endophenotypes for ADHD.

(2) Pharmacological approach: we examined the effect of atomoxetine on EF and VM in 30 drug-naïve boys with ADHD, aged 8-16, in an open-label trial after 12-week treatment. In addition to improvement in clinical and social functions, results showed significant improvement in EF and VM after treatment with atomoxetine for 4

weeks or 12 weeks. Our findings suggest that atomoxetine is effective in improving EF and VM among boys with ADHD.

(3) Neuroimaging approach: using 25 children with ADHD and 25 matched controls, we examined the association between the integrity of FS tracts and EF. The FS reconstructed by DSI tractography were subdivided into four segments, including dorsolateral, medial prefrontal, orbitofrontal, and ventrolateral tracts. Children with ADHD had lower generalized fractional anisotropy of all the bilateral frontostriatal fiber tracts. ADHD symptom severity and EF performance significantly correlated with integrity of the FS, particularly the left orbitofrontal and ventrolateral tracts.

(4) Genetic association approach: (a) we recruited a Chinese family-based sample (n = 906), and screened 15 polymorphisms across the DAT1 gene, including 14 SNPs and the variable number of tandem repeat (VNTR) polymorphism in 3′-untranslated region (3′UTR). Calculations of pairwise LD revealed three main haplotype blocks (HBs). Haplotype analysis showed that a haplotype rs27048 (C) /rs429699 (T) was significantly associated with the inattentive subtype. Our findings indicate that the *DAT1* gene may primarily affect the inattentive subtype of ADHD.

(b) We extended the family-based sample (n = 1298) and examined the association between *DAT1* and EF. Haplotype-based association tests showed that a haplotype rs403636 (G) /rs463379 (C) /rs393795 (C) /rs37020 (G) in HB1 was significantly associated with SWM errors. Our findings indicate that *DAT1* plays a role in the SWM errors of ADHD.

In summary, in addition to EF, we identified VM as potential endophenotype for ADHD and found significant effects of atomoxetine on EF and VM. We demonstrated that EF was linked to disturbed integrity of frontostriatal tracts and variations of the DAT1 gene. Further pharmacogenetic and imaging genetic studies are needed to establish the pathophysiological pathways underlying ADHD.

1. 緒論 (Introduction)

前言

在兒童青少年的精神疾病中，過動症是一個常見的臨床問題。「過動症」的全名為「注意力不足過動症」（Attention-Deficit/Hyperactivity Disorder，簡稱 ADHD）。ADHD 對個人的學業、工作及人際關係、家庭的壓力和社會經濟的衝擊極大。造成 ADHD 的原因目前雖然沒有定論，但是基本上研究發現主要的問題是來自基因遺傳的變異，造成孩子有不專心、過動、與衝動等症狀。另外在神經生物學方面會有神經心理學與神經影像學方面的異常。本文將針對 ADHD 臨床症狀與診斷、流行病學研究、基因遺傳學、神經心理學、神經影像學、以及藥物治療等層面加以探討。

1.1 注意力不足過動症的臨床症狀、診斷、與流行病學研究

ADHD 的主要核心症狀是不專心、過動和衝動。不專心方面，包括: 沒有注意到細節、粗心大意、無法持續注意力於較枯燥重覆的內容、注意力分散、別人對他講話時心不在焉、沒耐心聽完指示或吩咐、需要不停地提醒日常生活的事情、弄丟常用的東西、沒有時間觀念。過動方面，包括: 跑來跑去、爬高爬低、不怕危險、精力旺盛、不覺得累、坐不住甚至於離開位子、坐時身體扭來扭去、動來動去或玩弄手指。這些孩子會動作比較粗魯，運動協調不佳，常會有意無意地碰觸別人，肢體動作蠻多的，容易惹人厭或被誤會打人。且他們可能會比較愛講話，例如在不適合的情況下，在吃飯時或應該安靜的情境下，已經被提醒了不該講話，可能忍不住，幾分鐘之後又開始繼續講話，難以控制不講話。衝動方面，包括: 沒有耐心、不管別人多忙或別人在談話，他會打斷人家或是插嘴；別人對他說話時他也會沒有耐心聽別人講完，會接話或急著回答；對於很多事情可能會好管閒事、熱心過度，常會替別人出意見，當別人不聽他的意見時就會產生衝突

或不愉快；相對地，他也比較容易沒有耐心，不願意排隊買東西或玩，比較難與他人輪流，即使不得不排隊，他也會表現出比較不耐煩或不高興的樣子。整體來講，這些孩子因為其特徵會造成其學業表現不如其該有的能力，且有明顯人際上的問題，不管在同儕方面或是與父母、老師。在行為上可能會有一些不遵守規定、衝動或干擾別人的行為 (Fischer et al., 1990)。

目前診斷的兩大系統是 ICD-10 （國際疾病分類第 10 版），是國際衛生組織的版本（Hyperkinetic Disorder），另一個則是美國的 DSM-IV （注意力不足過動症，Attention-Deficit/Hyperactivity Disorder，AD/HD，APA 1994）。基本上這兩大系統所涵蓋的行為特徵大致上是相同的，主要的差異是在有無診斷亞型。DSM-IV 有較寬廣的定義，在九項不專心的症狀中要有六項，過動與衝動的九項中要有六項才符合診斷，同時符合這兩大症狀群，才符合混合亞型 （Combined Type），若症狀數只有符合不專心或過動/衝動症狀群之一，則為不專心亞型（Inattentive Type）或過動/衝動亞型 （Hyperactive-Impulsive Type）。ICD 則是採取較狹隘的定義，注意力、過動和衝動三種症狀群要同時出現才符合，並且將話多放在衝動的部分，因此在九項不專心症狀中要有六項，五項過動症狀要符合三項，四項衝動症狀至少要有一項才符合診斷。兩個診斷準則都要求這些症狀要同時出現在兩種情境以上，若只是出現在一種情形，可能不是過動症造成的。

ADHD 是一個早發性的精神疾病，一出生就存在，只是在不同時期發現。在 DSM-IV 和 ICD-10 的診斷準則都要求症狀必須在 7 歲以前就明顯被觀察到，甚至有研究認為在五歲以前就應有明顯症狀，才可下診斷。這兩個診斷系統各有優缺點，選擇嚴格或較寬鬆的定義取決於臨床或研究的需要，許多臨床醫師會選擇 DSM-IV 的診斷系統因為可以早期發現需要治療的兒童，而不會錯估需要治療的個案。診斷上以二分法來判定是否是有過動症，如果考慮到症狀改善的程度及治療效果，可能會以症狀群看其症狀嚴重程度的改變來作評估，在觀察治療的療效部分，可考慮以多面向或亞型的方式評估症狀的改變。

往往一次的初診觀察和評估是不夠的，應該追蹤幾次以確定診斷；評估時

要考慮孩子的心智發展應有的表現，仔細評估其行為表現是否異於同年齡的孩子，設法對出現的症狀提出其他替代性解釋，以及盡量找出任何重大的共病症狀，以免誤診其他身體或精神疾病為 ADHD。目前還沒有診斷 ADHD 的心理測驗。因此，必需藉助智力、注意力測驗、自填式問卷、和會談以評估 ADHD，但是臨床的評估與診斷仍是國際上最為被接受診斷 ADHD 的方式。評估工具中的自填量表或是會談量表以及腦神經心理學測驗常被用來作為診斷上輔助之用或研究用途，可協助確立複雜個案的診斷。即使是國際知名且已被接受之評估工具仍皆需建立本土之常模與信效度，所有的評估也需以此為標準。目前台灣發展出的中文版量表包括：柯能氏父母版行為量表 （CPRS-R:S） 及柯能氏老師版行為量表 （CTRS-R:S） 以及父母和老師所填寫的 SNAP-IV，而這些中文量表的信效度已經獲得國際學術界的肯定 (Gau et al., 2009; Gau et al., 2008; Gau et al., 2006)。

ADHD 是遍布世界各國且盛行率相當高的疾病。以目前 DSM-IV 的診斷系統來看，學齡期孩子的盛行率大約是 5~10%，成人期則有 4%左右。過去由於使用的評估方法不同 （自填問卷、臨床診斷、精神科診斷會談）、工具不同 （各種版本的問卷、精神科診斷會談量表）、診斷系統不同 （ICD-9、ICD-10、DSM-III、DSM-III-R、DSM-IV）、以及個案來源不同 （臨床、社區、不同種族）會出現不同的盛行率，範圍從 0.5~17.1%不等。例如 DSM-III-R 的診斷系統其盛行率大約是 3~5%，改用 DSM-IV 後盛行率便提升許多，因為 DSM-IV 的定義較廣泛，涵蓋三個診斷亞型，大部分研究發現，合併亞型約佔 50~55%，不專心亞型約 30~35%，過動/衝動亞型約 15~20%。

至於在台灣的流行病學研究，我們使用標準診斷會談工具，以國中一年級學生為樣本，用二階段法所推算 ADHD 的盛行率是 7.5% (Gau et al., 2005)。調查國小到國中學生的 ADHD 研究是使用中文本 SNAP-IV，根據原先以 DSM-IV 的診斷準則或是以 95 百分比來決定是否有 ADHD，其盛行率約 7~8% (Gau et al., 2008)，若是以老師版報告為準，其盛行率可達到 8~12% (Gau et al., 2009)。

1.2 注意力不足過動症的神經認知功能障礙

1.2.1 神經認知功能障礙

　　神經心理學是藉由神經心理測驗來評估人類的知覺、認知、與行為等腦部功能，而過去的神經心理學研究發現 ADHD 的行為問題是由於腦部功能異常所導致，目前研究顯示與 ADHD 最有關連性的神經心理功能障礙是執行功能（executive function）的異常 (Willcutt et al.,2005)。執行功能的定義是讓個體在新的環境與多種反應的選擇下完成目標導向 （goal-directed） 的認知功能，因此執行功能並非單一的認知功能，而國外研究顯示與 ADHD 最有關連性的執行功能包括：抑制功能、規則轉換、工作記憶、與計畫能力等 (Pennington & Ozonoff, 1996)，而 ADHD 的執行功能障礙可能會導致患者在學業與人際互動的障礙 (Faraone et al., 2000)。根據過去執行功能的研究，ADHD 患者在視覺空間 (visuo-spatial) 的障礙比語言 (verbal) 的障礙要更加顯著 (Martinussen et al., 2005)，此外，與對照組相比，若是測驗的難度增加時，ADHD 患者的執行功能障礙會變的更加明顯 (Young et al., 2007)。

　　有些因子會影響 ADHD 患者的執行功能，包括智能、發展階段、藥物、以及精神疾病的共病 (comorbidity) 等，而這些因子是否能完全解釋 ADHD 的執行功能障礙，或者 ADHD 本身就會伴隨有執行功能的障礙，這是過去相當受到關注的議題，根據統合分析 (meta-analysis) 的研究，即使在控制智能、閱讀能力、以及精神疾病的共病後，ADHD 患者仍有顯著的執行功能障礙 (Willcutt et al., 2005)。另外相對於過動或衝動的症狀，ADHD 患者的執行功能的障礙似乎會持續較久的時間 (Barkley, 2004)，過去研究已顯示成人 ADHD 患者仍然會有執行功能的異常 (Muller et al., 2007)，而 Biederman 等人在十年的長期追蹤研究發現，即使 ADHD 的症狀已隨時間有逐步改善，但執行功能障礙卻仍然持續存在 (Biederman et al., 2009)，表示執行功能障礙可能是一項特質標記 (trait marker)，

過去的研究顯示使用 methylphenidate 可以改善 ADHD 的執行功能 (Coghill et al., 2007)。另外在進行 ADHD 的神經心理功能研究時應注意 ADHD 的發病年紀，因為過去有研究顯示晚發病的 ADHD 在語言智商 (verbal IQ) 與操作智商 (performance IQ)，其表現都會比早發病的患者來得差，可能表示發病年紀會影響 ADHD 患者的神經心理功能 (Faraone et al., 2006)。

雖然過去認為 ADHD 患者執行功能的障礙會從兒童期一直持續到青少年期，但對於青少年 ADHD 患者的執行功能研究仍然不多，而且現有的研究結果彼此之間也有很大的差異性，舉例來說，Barkley 等人發現青少年 ADHD 患者並沒有明顯的工作記憶或反應抑制 (response inhibition) 方面的障礙 (Barkley et al., 2001)，因此對於青少年 ADHD 患者的執行功能應該需要進一步的研究。

1.2.2 神經認知內表現型

另外一個與神經心理功能有關的議題則是內表現型 （endophenotype）。有別於傳統以行為特徵定義 ADHD 的表現型，近年來研究傾向找出 ADHD 的內表現型，以便更接近造成 ADHD 的致病原因。內表現型的定義是指比症狀和表徵更接近某臨床疾病的生物學病因之表現型，而受和此疾病同樣的一個或多個易受性基因的影響。ADHD 內表現型必須符合以下的要求 (Doyle et al., 2005)：(1) 和 ADHD 同時存在，但是不能在有 ADHD 診斷的患者一定存在此內表現型，也就是說有高於一般人的比例在 ADHD 患者出現此內表現型，但不必然 ADHD 患者一定存在此表現型;(2) 可以被具有良好計量特質 （包括信效度）的測量工具所測量; (3)必須要有遺傳的證據; (4) 和 ADHD 要有家族性及基因的重疊，若沒有家族聚集性重疊，研究者可能找到生物學表現型基因，但是無法找到 ADHD 的基因。一般而言，神經心理功能、神經影像、以及神經電生理等方面都可以作為 ADHD 的內表現型，但在這些內表現型中，神經心理功能相對是價格比較便宜，而且沒有侵入性檢查的危險，因此已被 ADHD 相關研究學者認為是最適合作為

研究 ADHD 的內表現型 (Doyle et al., 2005)。

由前述 1.2 (a)的段落我們可以知道，ADHD 患者會合併有執行功能的障礙，因此執行功能障礙也被認為是 ADHD 可能的內表現型之一。過去研究顯示，執行功能的遺傳率 (heritability) 為 0.72 (Fan et al.,2001)，因此是一種會有家族遺傳性的神經心理學功能障礙。另外，除了 ADHD 患者本身具有執行功能的障礙，過去的研究也發現，在 ADHD 患者家庭，未患有 ADHD 的親屬中也有注意力控制 (D. I. Slaats-Willemse et al.,2007) 和反應抑制 (D. Slaats-Willemse et al., 2003) 方面的異常，在領養研究(adoption studies)中，與養父母相比較，ADHD 患者的生父母被發現在視覺注意力 (visual attention) 與反應時間 (reaction time) 的表現較差 (Alberts-Corush et al., 1986)，另外 Nigg 等人的研究則發現，ADHD 患者的生父母在視覺空間定向作業 (visuospatial orienting task) 有較差的反應 (Nigg et al., 1997)，由上述的研究可以推論 ADHD 和執行功能障礙具有家族重疊性。但也有的研究報告並未發現ADHD 患者的親屬有執行功能方面的異常 (Asarnow et al., 2002; Murphy & Barkley, 1996)，這可能是因為過去的研究主要都是只用單一測驗來評估執行功能，缺乏使用完整的標準化工具來評估 ADHD 患者其未發病親屬的整體執行功能。

在神經心理功能方面，除了執行功能可以作為 ADHD 的內表現型之外，另外一個可能的內表現型是視覺記憶 (visual memory)。過去研究顯示 ADHD 患者有很明顯的記憶功能障礙 (Rapport et al., 2001)，而視覺記憶是指受試者在看完一個複雜的圖形之後，必須將圖形記住，之後要藉著回憶選取正確的圖形配對，因此視覺記憶對於受試者是一個需要高度運用心思才能完成的測驗 (Berman et al., 1999)。有幾方面的證據支持進一步研究視覺記憶可以作為 ADHD 的內表現型，第一，有愈來愈多的報告顯示 ADHD 患者同時合併有視覺記憶的障礙，包括空間辨認記憶 (spatial recognition memory) (Kempton et al., 1999)、延遲樣本配對 (delayed matching to sample) (Barnett, Maruff, & Vance, 2009)、形態辨認記憶 (pattern recognition memory) (S. M. Rhodes et al.,, 2004)、以及配對相關學習

(paired associates learning) (H. T. Chang et al., 1999)等方面，上述這些研究都支持 ADHD 患者的神經心理功能障礙包含了視覺記憶的問題；第二，內表現型必須要能遺傳，而過去研究顯示視覺記憶的遺傳率為 0.53，甚至高於語言和感官訊息處理速度的遺傳率 (Alarcon et al., 1998)；第三，methylphenidate 對於 ADHD 患者的視覺記憶障礙有明顯的改善效果 (S. M. Rhodes et al., 2004; S. M. Rhodes et al., 2006)。雖然有上述的研究支持視覺記憶可能是 ADHD 的內表現型，但到目前為止，世界上還沒有任何一個家族研究證實 ADHD 患者其未發病的親屬也同時有視覺記憶的障礙。

1.3 注意力不足過動症的內表現型與藥物治療

執行功能是 ADHD 可能的內表現型，而跟執行功能有關的神經傳導物質主要為 catecholaminergic 系統 (A. F. T. Arnsten & B.-M. Li, 2005)，因此透過作用在 catecholaminergic 系統的藥物，應該有可能改善 ADHD 執行功能的障礙。目前在台灣對於 ADHD 的治療藥物主要有兩種，一種是 methylphenidate，另外一種則是 atomoxetine。其中 atomoxetine 是一個高度選擇性的正腎上腺素再吸收抑制劑 (highly selective noradrenaline reuptake inhibitor)，不會作用於其它的神經傳導物質 (Simpson & Perry, 2003)。所以 atomoxetine 可以提高前額葉的正腎上腺素的濃度，但不會對於 nucleus accumbens 有任何影響 (Bymaster et al., 2002)，而 nucleus accumbens 是與神經興奮劑之成癮性相關的腦部區域 (Koob & Le Moal, 1997)，因此，atomoxetine 是第一個在 2002 年被美國 FDA 通過用來治療 ADHD 的非中樞神經興奮劑。而過去西方 (Caballero & Nahata, 2003) 和台灣 (Gau et al., 2007) 的研究均顯示，atomoxetine 可以有效改善 ADHD 的臨床症狀，同時也不會對於睡眠產生不良的影響 (Prasad & Steer, 2008)，atomoxetine 對於 ADHD 共病有抽搐 (Allen et al., 2005) 和焦慮 (Geller et al., 2007) 的患者也有比較好的療效，因此 atomoxetine 在 ADHD 的臨床治療上扮演十分重要的角色。

Faraone 等學者建議執行功能障礙也應該被視為 ADHD 的治療目標之一 (S. V. Faraone et al., 2005)。雖然過去研究顯示執行功能與 catecholaminergic 系統中的正腎上腺素有關 (L. A. Newman, Darling, & McGaughy, 2008)，但目前只有很少研究探討 atomoxetine 對於 ADHD 執行功能障礙的療效。動物的研究顯示 atomoxetine 可以改善反應時間 (five-choice serial reaction time) (Blondeau & Dellu-Hagedorn, 2007)、降低衝動性 (Robinson et al., 2008)、以及改善注意力 (L. A. Newman et al., 2008)。人類的研究則發現，atomoxetine 可以減少健康受試者 (Samuel R. Chamberlain et al., 2006) 與成人 ADHD 患者 (S. R. Chamberlain et al., 2007) 之停止訊號的反應時間 (stop-signal reaction time)，另外對於成人 ADHD，在經過三週 (T. Spencer et al., 1998) 和十週 (S. V. Faraone et al., 2005) 的 atomoxetine 治療之後，患者的抑制能力會顯著增加。但過去有限的資料也顯示，atomoxetine 對於成人 ADHD 患者持續的注意力 (sustained attention) (T. Spencer et al., 1998)、注意力轉換作業 (attentional set shifting) (T. Spencer et al., 1998)、以及空間工作記憶 (spatial working memory) (S. R. Chamberlain et al., 2007)並沒有明顯的改善效果。

雖然臨床上服用 atomoxetine 的兒童 ADHD 患者愈來愈多，但十分缺乏探討 atomoxetine 對於兒童執行功能作用的研究，僅有一篇先驅研究發現 atomoxetine 對於兒童 ADHD 患者的快速視覺訊息處理測驗 (Rapid Visual Information Processing task) 具有改善的效果 (Barton et al., 2005)，雖然前述的研究也同時評估患者其它的執行功能，如注意力轉換作業 (attentional set shifting)、空間計畫能力 (spatial planning)、以及反應時間 (reaction time)，但作者並未提到 atomoxetine 對於這些執行功能的療效是如何，此外，由於這個先驅研究只有收集了九名患者，受限於樣本數較少、檢定力 (power) 不足的緣故，所以其研究結果並無法對於 atomoxetine 在兒童 ADHD 患者的執行功能療效上做出肯定的結論，只以編者來信發表，未來仍需要更大規模的研究來探討 atomoxetine 對兒童 ADHD 患者執行功能障礙的療效。

除了執行功能障礙之外，前述 1.2 (b) 節的段落亦已描述 ADHD 患者可能同時合併有視覺記憶障礙，而過去的研究顯示視覺記憶可能與中樞神經的正腎上腺素系統具有相關性，因為中樞神經正腎上腺素的釋放會提升記憶能力 (Gibbs, 2008)，動物的研究則顯示當受試動物在進行空間記憶 (spatial memory) 測驗時，正腎上腺素的濃度會同步增加 (Rossetti & Carboni, 2005)，表示正腎上腺素可能在視覺空間訊息 (visuo-spatial information) 儲存的能力上扮演重要角色，另外 Clayton 等人發現當活化老鼠中樞神經的正腎上腺素系統時，可以大幅改善視覺記憶的能力 (Clayton & Williams, 2000)。至於在人類的研究方面，Moor 等人發現若給予健康受試者靜脈注射正腎上腺素，會顯著提升其視覺辨認記憶 (visual recognition memory) 能力 (Moor et al., 2005)。除此之外，正腎上腺素也與注意力有密切的關係 (J. T. Coull et al., 2004)，若是大腦皮質的正腎上腺素濃度不足，將會導致明顯的注意力不足的現象 (Carli et al., 1983)。

雖然正腎上腺素在視覺記憶方面扮演重要角色，但過去並沒有相關文獻探討 atomoxetine 對人類視覺記憶的作用，只有少數的幾篇動物研究顯示，atomoxetine 可以減少視覺辨認記憶 (Tzavara et al., 2006) 以及視覺區辨測驗 (visual discrimination test) 的錯誤率 (Seu et al., 2009)，因此有必要進行研究以探索 atomoxetine 對於兒童 ADHD 患者視覺記憶障礙的治療效果。

1.4 注意力不足過動症的執行功能障礙與神經影像學

關於 ADHD 的影像學研究發展，常見的研究方式可分為結構性及功能性影像學研究，結構性研究常以 MRI （核磁共振） 分析腦部體積、皮質厚度，而新的擴散張量造影 (diffusion tensor imaging，DTI) 技術可以分析白質的神經束聯結。功能性研究常以 PET （正子造影） 或 fMRI （功能性核磁共振） 分析腦部血液灌流的變化，以間接得知神經活動的狀態。許多結構性研究一致地發現 ADHD 患者許多腦區的體積較正常人小，包括大腦的前額葉 (prefrontal cortex)

(Castellanos et al., 2001)、尾核 (caudate) (Castellanos et al., 2001; Castellanos et al., 2002)、蒼白球 (pallidum) (Castellanos et al., 1996)、背前側扣帶皮質 (dorsal anterior cingulate cortex) (dACC) (Larry J. Seidman et al., 2005)及胼胝體（corpus callosum) (Larry J. Seidman et al., 2005)，以及小腦的後下葉 (posterior inferior lobules)及蚓部 (vermis) (Castellanos et al., 1996)。最近的研究顯示 ADHD 的大腦皮質成熟較晚，因為一般兒童額葉大腦皮質的厚度大約在 7 到 8 歲左右會達到頂端 (peak)，但 ADHD 的額葉皮質厚度大約要到 11 歲左右才達到頂端，而到了青少年時期，一般人的大腦皮質會開始變薄，但是 ADHD 患者若沒有接受治療，其大腦皮質變薄的速度會更快 (Shaw et al., 2009)，因此 ADHD 的患者在腦部發展方面確實有明顯的異常變化。

雖然 ADHD 可能與腦部許多區域的異常有關，其中最重要的區域為前額葉，同時前額葉也在人類的執行功能方面扮演重要的角色 (Arnsten, 2009)。根據神經解剖學的位置，前額葉又可以細分成四個功能上不同的區域，包括了背外側前額葉皮質 (dorsolateral prefrontal cortex，DLPFC)、內側前額葉皮質（medial prefrontal cortex，MPFC)、眼窩額葉皮質（orbitofrontal cortex， (OFC)、以及腹外側前額葉皮質（ventrolateral prefrontal cortex，VLPFC)，其中 DLPFC 與行動的計畫 (action planning) 有關 (Fuster, 2002)，MPFC 與在新奇情境下的注意力轉移 (shifting under novel situations) 有關 (Konishi et al., 2010)，OFC 與報償引導的行為 (reward-guided behavior) 有關 (Price, 1999)，VLPFC 則與空間訊息的處理 (spatial information processing) 有關 (Wolf et al., 2009)。

最近由於核磁共振技術的發展，DTI 可以提供更多關於腦內神經纖維束的走向及完整性的資訊，以致能夠直接呈現腦部區域之間的結構上的聯結，而在 DTI 的研究中 fractional anisotropy (FA)就經常被用來作為大腦白質細微結構的完整性 (microstructure integrity) 的指標 (Johansen-Berg & Behrens, 2009)。之前的 DTI 研究發現在額葉紋狀體 (frontostriatal tracts) (Ashtari et al., 2005; Casey et al., 2007; A. Konrad et al., 2010; Pavuluri et al., 2009)、小腦 (Ashtari et al., 2005)、皮

質脊柱路徑 (corticospinal tract) (Hamilton et al., 2008)、以及上縱行纖維束 (superior longitudinal fasciculus) (A. Konrad et al., 2010)等區域，兒童及青少年 ADHD 患者的白質細微結構的完整性有缺損。在上述這些 ADHD 患者可能出現神經聯結缺損的腦部區域中，以額葉紋狀體的神經聯結缺損為最一致性的發現 (Liston et al., 2011)。除了與 ADHD 的診斷有相關之外，也有研究進一步發現紋狀體的 FA 數值與兒童 ADHD 患者的症狀嚴重程度有關。

只有少數的研究探討額葉紋狀體神經聯結與執行功能之間的關係，Liston 等人發現額葉紋狀體神經聯結的成熟會提升健康受試者在完成 go/no-go task 的效率 (efficiency) (Liston et al., 2006)，另外 Casey 等人的研究也發現，額葉紋狀體的 FA 數值愈高，兒童 ADHD 患者在進行 go/no-go task 時的衝動性會下降 (Casey et al., 2007)，fMRI 也顯示額葉紋狀體的活化與 ADHD 患者的執行控制 (executive control) (K. Konrad et al., 2006) 以及作業轉換 (task switching) (Dibbets et al., 2010) 有關。

目前對於 ADHD 患者的執行功能障礙的神經結構缺損機轉還在初步研究的階段，而且 DTI 的訊號可能會受到神經纖維交叉 (crossing fibers) 的干擾，以致無法正確評估神經聯結的完整性，因此未來仍需要更高解析度的核磁共振的技術，以便能更深入地探討額葉紋狀體在 ADHD 患者的執行功能障礙所扮演的角色。

1.5 注意力不足過動症的基因遺傳學

1.5.1 *DAT1* 基因與注意力不足過動症的相關性研究

ADHD 屬於複雜的遺傳性疾病，也就是說 ADHD 可能和很多基因都有關聯性，這些個別的基因雖然不會直接導致疾病，但會增加或減少罹病的機會，而 ADHD 可能是這些基因與各種環境因子交互作用所產生的結果。目前的相關性分析的研究顯示的可能候選基因 (candidate gene) 種類非常多，但集中在兩個主

要的神經傳導系統：多巴胺 (dopamine) 系統，及正腎上腺素 (norepinephrine) 系統，其中 DAT1 是最常被提到的 ADHD 候選基因。

DAT1 基因位於染色體 5P15.33，由 15 個外顯子 (exons) 與 14 個內顯子 (introns) 所組成，大小約為 52kb，有幾方面的證據支持 DAT1 是 ADHD 的致病基因：第一，目前治療 ADHD 的藥物中使用最多的是中樞神經興奮劑 methylphenidate，而 methylphenidate 就是藉著阻斷 dopamine transporter (DAT) 以達到治療效果 (Volz, 2008)；第二，過去神經影像學研究顯示在兒童 ADHD 個案的腦部 DAT 密度比健康對照組高 50% (Cheon et al., 2003)，另外也有研究顯示成人 ADHD 個案的腦部 DAT 密度比健康對照組高 17% (Dresel et al., 2000)；第三，在使用 methylphenidate 治療了三週之後，ADHD 個案的腦部 DAT 密度下降大約 74.7% (Vles et al., 2003)，在停止使用 methylphenidate 之後，DAT 的密度上升了 64% (Feron et al., 2005)；第四，DAT1 konck-out 的老鼠可以作為 ADHD 合適的動物模式 (Trinh et al., 2003)。綜合以上幾方面的證據，支持 DAT1 基因確實是 ADHD 的重要候選基因。

過去的研究主要集中在 DAT1 基因在 3´-untranslated region (3'UTR)的變異 (variable number of tandem repeat，VNTR)，因為這個位置的基因變異與精神疾病具有顯著相關性，包含精神分裂症 (Prata et al., 2009) 與酒精依賴 (Samochowiec et al., 2006)。雖然 Cook 等人在 1995 年第一次發現 DAT1 基因的 3´VNTR 與 ADHD 具有明顯的相關性 (Cook et al., 1995)，但後續的研究並沒有顯示一致性的發現 (Stephen V. Faraone et al., 2005; D et al., 2006; Purper-Ouakil et al., 2005)。至於在華人的族群，有兩個研究分別顯示 DAT1 基因的 3´VNTR 的 10-repeat (Chen et al., 2003) 及 11-repeat (Qian et al., 2004) 與 ADHD 之間具有顯著相關性，但其它兩個研究並不支持這樣的相關性 (Cheuk, Li, & Wong, 2006; Wang et al., 2008)。

一些因素可能可以解釋在上述這些研究結果之間的異質性，第一，過去研究顯示 ADHD 個案是否同時有其他精神科共病疾病 (comorbidity)，會影響

ADHD 與 DAT1 的相關性 (Zhou et al., 2008)，因此不同的 ADHD 研究所納入的個案具有不同的共病精神疾病，將會影響與 DAT1 之間的相關性分析；第二，由於 ADHD 本身的外在表現型 (phenotypes) 具有相當大的異質性，例如 ADHD 可以分成注意力不足亞型 (inattentive subtype)、過動與衝動亞型 (hyperactive-impulsive subtype)、以及混合型 (combined subtype)，過去的研究顯示若是將 ADHD 診斷縮小範圍至某一特定的亞型，將可以增加發現候選基因的機會 (Genro et al., 2008; Waldman et al., 1998)。

DAT1 的 3'VNTR 可能與其它鄰近的基因變異形成連鎖不平衡 (linkage disequilibrium，LD)，因此在進行 ADHD 的分子基因研究時，應考慮 DAT1 基因上的 LD 結構 (Greenwood et al., 2002)，雖然過去許多研究都在探討 DAT1 基因與 ADHD 的相關性，但其中只有少數研究有報告整個基因的 LD 結構，一項結合了八個國家的大規模研究顯示，ADHD 個案的 DAT1 基因在 LD 結構上有四個單套體區間 (haplotype blocks)，而在德國 (Friedel et al., 2007) 與巴西 (Genro et al., 2008) 的研究則顯示了三個單套體區間。在任何一個特定的族群裡面，突變、基因漂移 (genetic drift)、以及種族的融合等因素都可能會影響 LD 結構，因此在不同的族群可能會有不同的 LD 結構，根據我們所知，過去並沒有任何 ADHD 的基因研究探討 DAT1 在華人族群的 LD 結構。

除了上述所提到的 3'VNTR，少數的研究曾經探討 DAT1 基因上的其它單核苷酸多型性 (single nucleotide polymorphism，SNP) 與 ADHD 之間的相關性，例如 Brookes 等人曾報告 rs40184 與 ADHD 之間具有相關性 (Brookes et al., 2006)，但 Genro 等人的研究則不支持這樣的結果 (Genro et al., 2008)，另外，Friedel 等人則報告 rs27072 與 ADHD 之間具有相關性，而在 Gizer 等人的 meta-analysis 也顯示 rs27072 與 ADHD 之間的顯著相關性。

在進行 ADHD 的基因研究時還有一個重要的因素要加以考慮，因為像 ADHD 這樣的精神疾病一定不能只用單一基因變異來加以解釋，因此只鑑定單一基因變異只能提供非常有限的訊息，但是 DAT1 基因已經發現有許多的變

異，一個重要的問題是如何在這麼多的變異中選取有意義的標記來加以鑑定，並進一步分析這些標記與 ADHD 之間的相關性。若我們是以隨機的方式來選取要鑑定的基因變異，這並不是一個有效的方法，我們需要以科學與系統性的方法來選取可能有意義的基因變異，過去的研究顯示 haplotype-tagging SNP 的方法可以提供更完整又有效的途徑來鑑定基因上有意義的變異 (Kollins et al., 2008)，因為這種方法可以藉著研究 LD 的結構來減少不必要的基因鑑定，並增加更多的基因相關性訊息。

整體來說，雖然 DAT1 基因在 ADHD 的病理機轉上扮演重要的角色，但在不同的研究結果之間仍然存在明顯的差異性，並且基因的作用在不同族群之間可能有不同的影響，因此我們需要對於華人族群 DAT1 基因的 LD 結構加以研究，進一步可以藉由 haplotype-tagging SNP 的方法，以便全面性地探索 DAT1 基因在 ADHD 的病理生理機轉。

1.5.2 *DAT1 基因與執行功能障礙之相關性*

由於上述基因的研究顯示 DAT1 是 ADHD 的候選基因，我們進一步希望驗證 DAT1 是否會造成 ADHD 的執行功能障礙。有下列幾方面的證據支持 DAT1 基因與執行功能是有相關性的，第一，*DAT1* 基因剔除（knock-out) 的老鼠被發現合併有執行功能的缺損，例如空間工作記憶 (spatial working memory) (B. Li et al., 2010) 和反應抑制障礙 (Trinh et al., 2003)；第二，methylphenidate 藉著抑制 DAT 而提升神經突觸間的多巴胺濃度，而過去研究發現 methylphenidate 可以改善兒童 ADHD 患者的執行功能 (Vance et al., 2003)；第三，過去研究已顯示 DAT1 基因在健康兒童的執行功能-注意力神經網路 (executive attention network) 的發展扮演重要角色 (Rueda et al., 2005)；第四，影像基因學的研究證實在健康受試者的 DAT1 基因變異與工作記憶的神經反應具有顯著相關性 (Stollstorff et al., 2010)。綜上所述，探索 DAT1 基因與 ADHD 患者的執行功能

障礙之間關係的研究是十分具有價值的。

　　過去這方面的研究主要集中在 DAT1 基因的 3´VNTR 與執行功能障礙之間的關係，而這些研究結果彼此有很大的差異性 (Barkley et al., 2006; Karama et al., 2008; Loo et al., 2008; Wohl et al., 2008)，Karama 等人發現 DAT1 基因的 3´VNTR 與執行功能中的工作記憶與空間計畫有關 (Karama et al., 2008)，Cornish 等人則發現，若患者在 3´VNTR 帶有 10-repeat 的基因變異，則同時合併有較差的選擇記憶與反應抑制能力 (Cornish et al., 2005)，然而過去也有研究報告相反的結果，例如 Boonstra 等人發現 ADHD 患者若是帶有 10-repeat 的基因變異，反而會有比較好的執行功能表現 (Boonstra et al., 2008)，此外，也有研究指出 DAT1 基因的 3' VNTR 與 ADHD 患者的執行功能障礙之間並無相關性，包括注意力轉換作業 (Wisconsin Card Sorting Task) (Barkley et al., 2006)以及叫色作業 (Stroop Color-Word Task) (Loo et al., 2008; Wohl et al., 2008)。這些研究結果彼此之間的差異可能與幾方面的因素有關，例如 ADHD 患者的特性和所使用的神經心理學測驗等。此外，可能不是只有 DAT1 基因上的某一個變異就會造成 ADHD 患者的執行功能障礙，而是數個基因變異加成的效果才導致了執行功能的障礙，因此只有鑑定一個特定的基因型 (如 3' VNTR) 並無法完整探索 DAT1 基因在執行功能障礙所扮演的角色，也進而產生了過去研究結果彼此之間的差異性 (Mill et al., 2006)。

　　除了 3'VNTR 之外，只有很少數的研究去探討 DAT1 基因的其它變異與神經心理功能之間的關係 (Bellgrove et al., 2007; Kollins et al., 2008; Rommelse, et al., 2008)，Bellgrove 等人發現在健康受試者中，DAT1 基因第八個內顯子 (intron 8) 的 3-repeat 變異與空間注意力 (spatial attention) 有關 (Bellgrove et al., 2007)，在一份收集了 152 個 ADHD 家庭的研究報告指出，DAT1 基因上的四個 SNPs，包括 rs37020、rs464049、rs409588、以及 rs2042449 等，與持續注意力測驗 (Continuous Performance Task，CPT) 的表現有關 (Kollins et al., 2008)，但在另外一個收集了 350 位 ADHD 患者與 195 位未發病手足的家族研究中，Rommelse

等人則發現 DAT1 基因上的六個變異，包括 3' VNTR、intron 8、rs2550946、rs11564750、rs3776513、以及 rs40184 等，與執行功能之間並無顯著相關性 (Rommelse et al., 2008)，因此 DAT1 基因上 3'VNTR 以外的變異與執行功能障礙之間關係仍有待進一步研究。

整體而言，雖然有些研究發現 DAT1 基因與 ADHD 患者的執行功能障礙之間具有相關性 (Cornish et al., 2005; Karama et al., 2008)，但其他的研究並不支持這一結果 (Loo et al., 2008; Wohl et al., 2008)。因此對於 DAT1 基因在 ADHD 執行功能障礙所扮演的角色仍有待進一步的探討。

1.6 研究問題與假說

根據上述 ADHD 神經生物學的文獻回顧，我們提出下列的研究假說，希望能更進一步探討 ADHD 在神經心理學、內表現型、藥物治療、神經影像學、以及基因遺傳學等方面的研究議題，以期能更清楚掌握 ADHD 的病理機轉，並且希望未來能應用於 ADHD 患者的臨床評估與治療。

1.6.1 注意力不足過動症的執行功能障礙

1.6.1.1 研究問題：(a)ADHD 患者是否有較差的執行功能

(b)執行功能與視覺記憶是否為 ADHD 的內表現型

1.6.1.2 研究假說：

(a)

由於過去的研究主要是使用單一的測驗來評估 ADHD 患者的執行功能障礙，研究結果彼此之間缺乏比較性，也不易掌握 ADHD 患者整體的執行功能，因此我們設計的實驗是採用劍橋神經心理測驗 (Cambridge Neuropsychological Test Automated Battery，CANTAB)，這是一個空間、非語言的電腦測驗，包含

了完整的神經心理功能測驗,過去的研究已證實 CANTAB 在健康受試者中有很好的信效度 (Luciana & Nelson, 1998),並且可以應用於評估不同的精神疾病之認知功能,包括憂鬱症 (Purcell et al., 1997)、躁鬱症 (Sweeney et al., 2000)、精神分裂症 (Levaux et al., 2007)、失智症 (Egerhazi et al., 2007)、以及人格障礙症 (Dolan & Park, 2002)。對於我們所關注的執行功能,CANTAB 有四個分測驗是用來評估執行功能,包括 SSP、IED、SWM、以及 SOC,因此 CANTAB 可以完整地評估 ADHD 患者的整體執行功能。雖然過去西方有少數的研究使用 CANTAB 來評估 ADHD 患者的執行功能,並且發現患者在 SWM (Sinead M. Rhodes et al., 2004)、IED (Rhodes et al., 2005)、與 SOC (Kempton et al., 1999)等分測驗表現較差,但在華人族群並未曾經使用 CANTAB 來研究 ADHD 患者的執行功能。因此我們假設,與健康受試者相比,青少年 ADHD 患者的在 SSP、IED、SWM、以及 SOC 等 CANTAB 的執行功能分測驗的分數均較低。

(b)

過去雖然有研究探討 ADHD 患者之未發病的親屬之執行功能障礙,但研究結果彼此之間有很大的差異性 (Asarnow et al., 2002; Murphy & Barkley, 1996; D. Slaats-Willemse et al., 2003; D. I. Slaats-Willemse et al., 2007),這可能是由於過去的研究樣本不夠大,並且只使用單一工具來評估執行功能,以致無法有足夠的統計檢定力來探索 ADHD 患者之未發病親屬的整體執行功能。另外,前述的 CANTAB 是一個具有高度敏感性與精確性的神經心理評估工具,可以偵測出 ADHD 患者之未發病親屬細微的 (subtle) 執行功能障礙,但 CANTAB 過去並未曾使用於評估 ADHD 患者之未發病親屬。因此我們預計收集三組個案,包含 ADHD 患者、ADHD 患者之未發病手足、以及健康受試者,並且使用 CANTAB 的 SSP、IED、SWM、以及 SOC 等分測驗來評估三組個案的執行功能,我們假設 ADHD 患者將會有最嚴重的執行功能障礙,而 ADHD 患者之未發病手足的執行功能表現將會位於 ADHD 患者與健康受試者之間。

除了執行功能之外，現有的研究已顯示 ADHD 患者會合併視覺記憶的障礙，但過去並無任何研究探討 ADHD 患者之未發病親屬的視覺記憶功能，因此視覺記憶是否可作為 ADHD 的內表現型仍有待進一步驗證。我們使用 CANTAB 的視覺記憶分測驗，包含延遲樣本配對 (Delayed Matching to Sample，DMS)、空間辨認記憶 (Spatial Recognition Memory，SRM)、配對相關學習 (Paired Associates Learning，PAL)、以及形態辨認記憶 (Pattern Recognition Memory，PRM)，來評估前述三組個案的視覺記憶，我們假設 ADHD 患者將會有最嚴重的視覺記憶障礙，而 ADHD 患者之未發病手足的視覺記憶功能表現將會位於 ADHD 患者與健康受試者之間。

1.6.2 注意力不足過動症的內表現型與藥物治療

1.6.2.1 研究問題：atomoxetine 可否改善 ADHD 患者的執行功能與視覺記憶障礙

1.6.2.2 研究假說：

文獻回顧發現執行功能是 ADHD 的內表現型，但由於過去只有一個小型的先驅研究探討 atomoxetine 是否能改善兒童 ADHD 患者的執行功能障礙 (Barton et al., 2005)，因此仍有待進一步研究以評估 atomoxetine 對於兒童 ADHD 患者之執行功能的影響。我們將收集更多的兒童 ADHD 患者，並且使用 CANTAB 的 SSP、IED、SWM、以及 SOC 等分測驗，來探索在長期使用 atomoxetine 之後，兒童 ADHD 患者的執行功能是否有進步。我們假設，atomoxetine 不只能改善 ADHD 的症狀，也能改善患者的執行功能障礙。

除了執行功能障礙之外，我們的研究也發現 ADHD 患者會合併有視覺記憶障礙，並且視覺記憶可以做為 ADHD 的內表現型，因此我們使用 CANTAB 的 SRM 與 PRM 等分測驗，來探索在長期使用 atomoxetine 之後，兒童 ADHD 患

者的視覺記憶功能是否有進步。我們假設，atomoxetine 能改善患者的視覺記憶障礙。

1.6.3 注意力不足過動症的執行功能障礙與神經影像學

1.6.3.1 研究問題：額葉紋狀體神經路徑之完整性是否與 ADHD 之症狀和執行功能障礙有相關性

1.6.3.2 研究假說：

　　雖然文獻回顧中已有許多研究使用 DTI 的方法來探討 ADHD 患者的額葉紋狀體之白質細微結構的完整性，但目前仍未有研究使用擴散頻譜造影 (diffusion spectrum imaging，DSI) 的方法來研究 ADHD 患者的額葉紋狀體。相對於傳統的 DTI，DSI 能夠在腦部的神經聯結進行更完整的擴散性評估 (diffusion measurement)，以致 DSI 能夠有更好的角度解析度 (angular resolution) 來處理神經纖維交叉的問題，而目前 DSI 已經被證實可以有效地用來重建許多精神疾病的腦部神經路徑，包括強迫症 (Chiu et al., 2011)、酒精依賴 (I. C. Liu et al., 2010)、以及自閉症 (Lo et al., 2011)等。過去的研究顯示在神經纖維交叉的腦部區域，DTI 將會重建錯誤的神經纖維路徑 (false fiber pathways) (Wedeen et al., 2008)，顧名思義，額葉紋狀體的神經路徑是聯繫額葉到紋狀體之間的神經纖維，在神經解剖學上這條路徑會與許多其它的神經纖維束交叉，因此若使用傳統的 DTI 來重建額葉紋狀體的神經路徑，這將會是非常困難的工作，而且須要很多的手動操作 (manual editing) 以去除錯誤的神經路徑。相對地，若使用 DSI 來重建額葉紋狀體的神經路徑，除了可以有效地避免神經纖維束交叉的問題，而且還可以將額葉紋狀體的神經路徑作更精細的部位區分 (segmentation)，來探討此神經路徑與 ADHD 之間更具特異性 (specific) 的關係。此外，我們更進一步去分析 ADHD 的執行功能障礙與額葉紋狀體的神經路徑之間的關係。我們利

用 DSI 的方法將額葉紋狀體的神經路徑區分成四個部位，包括 caudate nucleus–DLPFC (dorsolateral)、caudate nucleus–MPFC (medial prefrontal)、caudate nucleus–OFC (orbitofrontal)、以及 caudate nucleus–VLPFC (ventrolateral)，並測量 ADHD 患者與健康受試者的一般性之部分異向性 (generalized fractional anisotropy，GFA)，我們假設，與健康受試者相比，ADHD 患者的這四條神經路徑之 GFA 較低，並且這四條神經路徑的 GFA 會與 ADHD 的執行功能障礙之間具有顯著的相關性。

1.6.4 注意力不足過動症的基因遺傳學

1.6.4.1 研究問題：(a) *DAT1* 基因是否與注意力不足過動症相關

(b) *DAT1* 基因是否與執行功能障礙相關

1.6.4.2 研究假說：

(a)

雖然 DAT1 基因在 ADHD 的病理生理機轉中扮演重要的角色，但過去的研究結果之間仍存在很大的差異性，特別是在華人的族群過去只針對 DAT1 基因上的某幾個變異做過探索，並未針對 DAT1 基因做過整體全面的研究，因此 DAT1 基因在華人族群的 ADHD 患者所扮演的角色仍有待確認 (Cheuk et al., 2006; Wang et al., 2008)。我們的研究將採用 haplotype-tagging SNP 的方法，來完整評估 DAT1 基因與 ADHD 之間的關係，而且我們也會將 ADHD 患者區分成不同的亞型 (subtype)，來探討 DAT1 基因與不同 ADHD 亞型的更特異的關係。我們假設，DAT1 基因上的變異不但與 ADHD 有相關性，而且與 ADHD 的症狀與亞型有相關性。

(b)

整體而言，雖然過去一些研究並未發現 DAT1 基因與 ADHD 患者的執行功能障礙有相關性 (Barkley et al., 2006; Loo et al., 2008; Rommelse et al., 2008; Wohl et al., 2008)，但也有研究證實 DAT1 基因與執行功能中的空間計畫 (the tower of London) 與工作記憶 (working memory) 有相關性 (Karama et al., 2008)，因此 DAT1 基因與 ADHD 患者的執行功能障礙之間的關係仍有待進一步的探討。而我們過去的研究已證實 DAT1 基因是 ADHD 的候選基因 (Shang et al., 2011)，而且在神經心理學研究中我們也證實了使用 CANTAB 來評估的執行功能障礙，包含 SSP、SWM、IED、以及 SOC 等方面，可以作為 ADHD 的內表現型 (Gau & Shang, 2010a)，其中又以 SWM 的效應值 (effect size)為最大，因此我們在這一個家族基因研究中將進一步探索 DAT1 基因與 ADHD 患者的執行功能障礙之間的關係。根據我們過去的內表現型研究，我們假設，DAT1 基因與 ADHD 患者的執行功能障礙，特別是 SWM 的表現，彼此之間會有顯著的相關性。

2. 研究方法與材料 (Materials and methods)

2.1 注意力不足過動症的神經認知功能障礙

2.1.1 神經認知功能障礙

2.1.1.1 受試者及步驟

本研究收集了 53 位 11 到 16 歲的青少年 ADHD 患者，其中 40 位為男性，13 位為女性，平均年齡為 12.7±1.4 歲，這些患者過去出現明顯 ADHD 症狀的平均年齡為 4.8±1.7 歲，第一次在臨床上被診斷為 ADHD 的平均年齡為 7.6±2.9 歲，另外我們也從患者的同一學區收集了 53 位健康受試者作為對照組，對照組的性別、年齡、智商、父母的教育程度均已與 ADHD 組配對，請見表 1。

母親與個案均分別接受精神科診斷性會談工具 the Kiddie epidemiologic version of the Schedule for Affective Disorders and Schizophrenia (K-SADS-E) 的評估，以確立其診斷。在 53 位 ADHD 患者中，有 29 (54.7%) 位診斷為混合亞型，17 (32.1%) 位為注意力不足亞型，7 (13.2%) 位為過動衝動亞型。受試者均接受 CANTAB 的神經心理測驗，此外，我們也選用智力測驗中 digit span 來評估個案的持續注意力和語言工作記憶。若是目前正在服用 ADHD 藥物的患者，則在接受測驗之前至少停止服用藥物 24 小時以上。收案的排除條件如下：有嚴重身體疾病如心血管疾病、全智商小於 80、雙極性情感性疾病病史、物質濫用病史、精神分裂症病史、廣泛性發展障礙症病史、或者癲癇病史等。

2.1.1.2 神經心理測驗：CABTAB

神經心理測驗是由臨床心理師根據 CANTAB 的標準流程加以施測，地點在台大醫院精神醫學部的神經心理檢查室，測驗的時間大約為 90 分鐘，我們選用 CANTAB 的四個分測驗以評估受試者的執行功能，以下分別介紹這四個分測驗：

Spatial Span (SSP). SSP 是評估受試者的空間短期記憶，一開始電腦螢幕上會出現數個固定位置的白色方格，之後每個方格會依照預設的順序，一個方格接著一個方格轉變顏色，受試者必須根據先前方格轉變顏色的順序來觸碰螢幕上的區域，測驗由兩個方格開始，最多至九個方格。最後有三個參數代表受試者的表現：(1) span length：能被成功回憶起的最長順序；(2) total errors：錯誤被選擇的方格總數；(3) total usage errors：受試者選擇一個不在被回憶順序的方格之次數。

Spatial Working Memory (SWM). SWM 是評估受試者的空間工作記憶，受試者被要求在螢幕上許多的方格裏尋找隱藏在其中藍色的方塊，受試者在發現藍色方塊後，必須用手指觸碰螢幕將方塊移至螢幕右方處，而每次測驗中一旦方格中的藍色方塊被找到後，這個方格就不會再出現任何藍色方塊，因此受試者必須一邊尋找新的藍色方塊，一邊牢記先前已出現藍色方塊的方格。最後有兩個參數代表受試者的表現：(1) strategy utilization：從新的方格開始搜尋的次數；(2) Errors in total and three different levels of difficulty：錯誤搜尋的總次數，以及在三個不同難度(4-, 6-, and 8-box problems)的錯誤搜尋次數。

Intra-dimensional/Extra-dimensional Shifts (IED). IED 是評估受試者的注意力轉換能力，電腦螢幕上會出現兩種不同特質的目標物，一個是線條，另外一個則是形狀，這個測驗依照難度總共有 9 個階段，一開始受試者必須根據形狀的特點來找出正確的規則，這是所謂的向度內轉換(intradimensional shifts，IDS)，接下來受試者必須轉移注意力至線條的特點來找出正確的規則，這是所謂的向度外轉換 (extradimensional shifts，EDS)，在整個測驗過程中受試者必須藉著試誤學習 (trial and error) 以找出正確的規則，而電腦一旦偵測到連續 6 次受試者正確的反應之後，規則將會自動轉換。最後有四個參數代表受試者的表現：(1)成功完成的 stages 數目；(2)為了完成 stages 所做的嘗試之總數；(3)在 EDS 之前的錯誤總數；(4)在 EDS 期間的錯誤總數。

Stocking of Cambridge (SOC). SOC 是評估受試者的空間計畫能力，一開始螢幕上會有兩列的色球，每一列有三個色球，上列色球的排列方式是下列色球的模

板 (template)，在移動色球之前受試者必須先在心中規畫，以便能用最少的移動次數將下列色球排列成上列色球的順序。上列色球的排列方式事先經過設計，根據難度的不同有 2、3、4、或 5 次的最少移動次數 (minimum number of moves)。最後有四個參數代表受試者的表現：(1)在不同難度的移動次數中成功解決的問題數目；(2)平均移動次數；(3)從受試者思考如何解決問題到開始移動第一個色球的時間；(4)從受試者開始移動第一個色球到完成問題的時間。

2.1.1.3 統計分析

描述性統計的部分以數目和百分比來顯示類別變項，以平均值和標準差來顯示連續變項。為了進行配對的病例對照研究，我們用條件式的邏輯回歸分析以比較患者組與對照組的精神疾病比率，並且以統計軟體 SAS 9.1 (SAS Institute Inc., Cary, NC, USA) 的 Proc Glimmix 指令來計算勝算比 (odds ratio，OR) 和 95%的信賴區間。對於連續變項，我們使用線性多階層模式 (linear multi-level model) 來比較兩組的 CANTAB 四個分測驗的分數，對於那些有不同難易程度的測驗 (SWM 和 SOC)，我們在檢驗組別與難易度的交互作用時會校正在同一個個案所進行的重複測量，Alpha 值設定在 0.05，我們使用 Cohen's d 的方法計算效應值 (effect size)，若 Cohen's d 大於 0.3 但小於 0.5 則為小 (small) 的效應值，若 Cohen's d 大於 0.5 但小於 0.8 則為中等 (medium) 的效應值，若 Cohen's d 大於 0.8 以上則為大 (large) 的效應值。

2.1.2 神經認知內表現型

2.1.2.1 受試者及步驟

本研究收集了 279 位 8 到 16 歲的兒童 ADHD 患者，其中 85.7%為男性，平均年齡為 12.5±1.6 歲，這些患者過去出現明顯 ADHD 症狀的平均年齡為 4.2±1.6 歲，第一次在臨床上被診斷為 ADHD 的平均年齡為 6.7±2.9 歲，同時我們收集

ADHD 患者未發病之手足共 108 人，平均年齡為 12.2±3.3 歲，另外我們也從患

者的同一學區收集了 173 位健康受試者作為對照組，平均年齡為 12.6±1.5 歲。

母親與個案均分別接受精神科診斷性會談工具 K-SADS-E 的評估，以確立

其診斷。受試者均接受 CANTAB 的神經心理測驗，此外，我們也選用智力測驗

中 digit span 來評估個案的持續注意力和語言工作記憶。若是目前正在服用

ADHD 藥物的患者，則在接受測驗之前至少停止服用藥物 24 小時以上。收案的

排除條件如下：有嚴重身體疾病如心血管疾病、全智商小於 80、雙極性情感性

疾病病史、物質濫用病史、精神分裂症病史、廣泛性發展障礙症病史、或者癲癇

病史等。

2.1.2.2 神經心理測驗：CABTAB

我們選用 CANTAB 的 SSP、SWM、IED、SOC 評估受試者的執行功能，並

以 DMS、PAL、SRM、PRM 評估受試者的視覺記憶功能，關於執行功能測驗請

見 2.1.1.2，以下則介紹視覺記憶的四個分測驗：

Delayed Matching to Sample (DMS). DMS 是評估受試者對於複雜且抽象的圖

形之記憶功能，在每一次測驗開始時，會有一個樣本圖形出現在螢幕中央約 4.5

秒，在同時情境 (simultaneous condition) 中，當樣本圖形仍在螢幕時，四個選項

圖形出現在螢幕下方；在延遲情境 (delayed condition) 中，樣本圖形先消失，之

後經過 0 秒、4 秒、或 12 秒之後，四個選項圖形才會出現在螢幕下方，受試者

要在選項圖形中選取一個與樣本圖形完全一致的圖形。最後有四個參數代表受試

者的表現：(1)偵測到錯誤發生的能力；(2)正確反應的平均時間；(3)在不同條件

下的正確反應數目；(4)在正確和錯誤反應之後出現錯誤的可能性。

Paired Associates Learning (PAL). PAL 是評估受試者在視覺圖形與視覺空間

的學習能力，在螢幕上會出現幾個方塊，這些方塊會依照隨機的順序而打開，而

有些方塊會包含圖形在其中，而這些方塊中的圖形之後會一個接著一個出現在螢幕中央，受試者必須依照中央的圖形去觸碰含有相同圖形的方塊。最後有三個參數代表受試者的表現：(1)錯誤發生的總數；(2)正確指出所有圖形時的錯誤總數；(3)第一次嘗試的記憶分數。

Spatial Recognition Memory (SRM). SRM 是評估受試者空間位置的辨認記憶能力，一開始有五個方塊在不同的位置依序出現，經過 5 秒之後，接下來受試者會一次看到兩個方塊，其中一個是在先前已經出現過的位置，但另一個是在先前並未出現過的位置，受試者必須辨認出哪一個方塊是位於先前已經出現過的位置。最後有兩個參數代表受試者的表現：(1) the percentage of correct responses：正確反應的百分比；(2) mean response latency for correct responses：正確反應的平均反應時間。

Pattern Recognition Memory (PRM). PRM 是評估受試者對形態圖形的辨認記憶能力，一開始有一系列不同形態的圖形依序出現，經過 5 秒之後，接下來受試者會一次看到兩個圖形，其中一個是先前已經出現過的形態，但另一個是先前並未出現過的形態，受試者必須辨認出哪一個圖形是先前已經出現過的形態。最後有兩個參數代表受試者的表現：(1) the percentage of correct responses：正確反應的百分比；(2) mean response latency for correct responses：正確反應的平均反應時間。

2.1.2.3 統計分析

描述性統計的部分以數目和百分比來顯示類別變項，以平均值和標準差來顯示連續變項。對於連續變項，我們使用線性多階層模式 (linear multi-level model) 來比較三組的 CANTAB 執行功能和視覺記憶的分數，對於那些有不同難易程度的測驗(SWM、SOC、DMS)，我們在檢驗組別與難易度的 interaction 時會校正在同一個個案所進行的重複測量。Alpha 值設定在 0.05，我們使用 Bonferroni 校正

多重比較的 p 值，此外我們也檢驗 CANTAB 的分數在三組是否有線性趨勢，我們會控制性別、年齡、全智商、精神疾病共病、ADHD 症狀、以及父母親教育程度，同時我們使用 Cohen's *d* 的方法計算效應值，若 Cohen's *d* 大於 0.3 但小於 0.5 則為小的效應值，若 Cohen's *d* 大於 0.5 但小於 0.8 則為中等的效應值，若 Cohen's *d* 大於 0.8 以上則為大的效應值。

2.2 注意力不足過動症的內表現型與藥物治療

2.2.1. 受試者及步驟

本研究收集了 30 位 8 到 16 歲未曾服用過藥物治療的男生 ADHD 患者，平均年齡為 10.70±1.84 歲，母親與患者均分別接受精神科診斷性會談工具 K-SADS-E 的評估，以確立其診斷。在 30 位 ADHD 患者中，有 15 (50%) 位診斷為混合亞型，13 (43.3%) 位為注意力不足亞型，2 (6.7%) 位為過動衝動亞型。有 11 位患者同時有其它精神科疾病共病，包括對立反抗性疾患 (36.7%)，行為規範疾患 (3.3%)，以及過去有焦慮疾患病史 (6.7%)。受試者均接受 CANTAB 的神經心理測驗。收案的排除條件如下：有嚴重身體疾病如心血管疾病、全智商小於 80、雙極性情感性疾病病史、物質濫用病史、精神分裂症病史、廣泛性發展障礙症病史、或者癲癇病史等。

2.2.2. 神經心理測驗：CABTAB

我們選用 CANTAB 的 SSP、SWM、IED、SOC、RVIP 評估受試者的執行功能，並以 SRM、PRM 評估受試者的視覺記憶功能，關於執行功能與視覺記憶測驗請見 2.1.2，以下則介紹 RVIP 測驗：

Rapid Visual Information Processing (RVIP).RVIP 是評估受試者的空間持續注意力，電腦螢幕中央一分鐘內會出 100 個數字，受試者必須根據偵測這些數字是

否有出現目標序列，3-5-7，2-4-6，4-6-8，若有出現則必須按下按鈕。最後有八個參數代表受試者的表現：(1) total hits：正確反應的次數；(2) total misses：應該反應卻不反應的次數；(3) total false alarms：不應該反應卻反應的次數；(4) correct rejections：正確拒絕反應的次數；(5) probability of hits：正確反應的百分比；(6) probability of false alarms：錯誤反應的百分比；(7) A'：偵測訊號的敏感度；(8) mean latency：正確反應的平均時間。

2.2.3. 統計分析

我們使用 180 位 8 到 16 歲健康發展兒童的 CANTAB 分數作為常模，將本研究 30 位 ADHD 患者的 CANTAB 原始分數轉換為 z 分數，其平均值設為 0，1 個標準差設為 1 個 z 分數。由於我們在同一個受試者進行多次測驗，因此我們使用線性多階層模式 (linear multi-level model)來比較用藥前與用藥後四週、以及十二週的 CANTAB 執行功能和視覺記憶分數差別。Alpha 值設定在 0.05，我們使用 Cohen's d 的方法計算效應值，若 Cohen's d 大於 0.3 但小於 0.5 則為小的效應值，若 Cohen's d 大於 0.5 但小於 0.8 則為中等的效應值，若 Cohen's d 大於 0.8 以上則為大的效應值。

2.3 注意力不足過動症的執行功能障礙與神經影像學

2.3.1. 受試者及步驟

本研究收集了 25 位兒童 ADHD 患者，另外我們也從患者的同一學區收集了 25 位健康受試者作為對照組，對照組的性別、年齡、慣用手、智商、父母的教育程度均已與 ADHD 組進行個人化的配對。

母親與個案均分別接受精神科診斷性會談工具 K-SADS-E 的評估，以確立其診斷。在 25 位 ADHD 患者中，有 18 (72.0%) 位過去曾服用藥物治療，所有

患者中 16 (64.0%) 位診斷為混合亞型，8 (32.0%) 位為注意力不足亞型，1 (4.0%) 位為過動衝動亞型。受試者均接受 CANTAB 的神經心理測驗與 MRI 掃描，若是過去曾服用 ADHD 藥物的患者，則在接受 MRI 掃描之前至少未服用藥物 1 週以上。收案的排除條件如下：有嚴重身體疾病如心血管疾病、全智商小於 80、雙極性情感性疾病病史、物質濫用病史、精神分裂症病史、廣泛性發展障礙症病史、或者癲癇病史等。

2.3.2. 神經心理測驗：CABTAB

我們選用 CANTAB 的 IED、RVIP、SWM、SOC 評估受試者的執行功能，關於執行功能測驗請見 2.1.1.2 及 2.2.2。

2.3.3. MRI 掃描

受試者接受 3T 的 MRI 掃描，在同一個 slice 同時收集 T2-weighted 與 DSI 的訊號，其中 T2-wighted 的 TR/TE = 5920 ms/102 ms，matrix size = 256×256，spatial resolution = 0.98 mm × 0.98 mm，slice thickness = 3.9 mm，而 DSI 的 TR/TE = 9100 ms/142 ms，image matrix size = 128×128，spatial resolution = 2.5 mm × 2.5 mm，slice thickness = 2.5 mm，總共有 102 個擴散梯度會被取樣，而擴散敏感度係數 bmax = 4000 s mm^{-2}，根據所收集的 DSI 數據我們算出取向分佈函數 (orientation distribution function，ODF)，我們可以再由以下公式算出一般性之部分異向性 (generalized fractional anisotropy，GFA) (Tuch, 2004)：

ODF 的標準差 / ODF 的平方根

接著我們將額葉紋狀體的神經纖維束藉由 5 個特定區域 (regions of interest，ROIs) (尾核、DLPFC、MPFC、OFC、和 VLPFC) 分成兩側各四條纖維束，也就是 caudate nucleus–DLPFC (dorsolateral)、caudate nucleus–MPFC (medial prefrontal)、caudate nucleus–OFC (orbitofrontal)、以及 caudate nucleus–VLPFC

(ventrolateral) 等神經路徑，我們使用 DSI 分析軟體，將 GFA 大於 0.1 的 voxel 選取為白質的區域，並且作為 seed voxel 以建立 tractography，沿著原本的神經纖維方向每次移動 0.4 個 voxel 的長度，以找到下一個起點，若是鄰近的 voxel 的角度偏移 (angle deviation) 大於 60 度，則自動停止搜尋神經路徑，而每條神經纖維束都取樣並使用 mean-path analysis algorithm 計算出平均一般性之部分異向性 (mean GFA)，至於腦部側化的指數 (lateralization index，LI)，則由以下公式計算：

LI = (左側神經束之 mean GFA–右側神經束之 mean GFA)/兩側神經束之平均 GFA

2.3.4. 統計分析

描述性統計的部分以數目和百分比來顯示類別變項，以平均值和標準差來顯示連續變項。為了進行配對的病例對照研究，我們使用線性多階層模式 (linear multi-level model)來比較兩組的 IQ、ADHD 症狀分數、CANTAB 四個分測驗的分數、GFA、以及 LI 等數據的平均值，對於 GFA，我們使用廣義線性模式 (general linear model) 來分析左右兩側、四條神經纖維束、以及兩組受試者的差別，Alpha 值設定在 0.05，我們使用 Cohen's d 的方法計算效應值，若 Cohen's d 大於 0.3 但小於 0.5 則為小的效應值，若 Cohen's d 大於 0.5 但小於 0.8 則為中等的效應值，若 Cohen's d 大於 0.8 以上則為大的效應值。

為了控制在多重單變項相關性時所產生的第一型誤差 (type I error)，我們使用多線性迴歸模式 (multiple linear regression models) 來檢驗兩側四條神經纖維束的 GFA 與 ADHD 症狀和執行功能之間的關係，我們將 GFA 作為自變項，ADHD 症狀和 CANTAB 執行功能測驗分數作為依變項，利用後退淘汰法 (backward elimination) 的方式找出最適合的模式，並且計算 R^2 代表模式所能預測的程度。

2.4 注意力不足過動症的基因遺傳學

2.4.1. *DAT1* 基因與注意力不足過動症的相關性研究

2.4.1.1. 受試者及步驟

本研究收集了 273 位 7 到 18 歲的青少年 ADHD 患者，其中 85.7%為男性，平均年齡為 10.8±2.5 歲，母親與個案均分別接受精神科診斷性會談工具 K-SADS-E 的評估，以確立其診斷。在 273 位 ADHD 患者中，有 65.2%診斷為混合亞型，28.9%為注意力不足亞型，5.9%為過動衝動亞型。同時我們也收集了患者的家族 DNA 樣本，其中 108 個家庭是一位初始患者 (proband)、一位手足、以及父母雙親，110 家庭是一位初始患者、以及父母雙親，7 個家庭是一位初始患者、一位手足、以及一位父親或母親，39 個家庭是一位初始患者、以及一位父親或母親，最後總樣本數為 906 人，在 133 位手足中 41.5%為男性，平均年齡為 11.5±3.8 歲，其中 58 位手足符合 ADHD 診斷，而 25.9%診斷為混合亞型，51.7%為注意力不足亞型，22.4%為過動衝動亞型。

2.4.1.2. 選取 SNP 與基因型鑑定

從公共資料庫 HapMap 中搜尋漢族華人的基因資料，並以下列條件作為選取 tag SNPs 的標準：(1) SNP 必須位於 DAT1 基因上；(2) SNP 的 minor allele frequency 大於等於 0.1；(3) 其它沒有被選取的 SNP 與 tag SNP 的 LD 相關係數大於等於 0.8。符合上述標準的 tag SNP 一共有 14 個 (rs2937639，rs2617605，rs393795，rs10052016，rs37020，rs40358，rs37022，rs466630，rs27048，rs429699，rs11133767，rs40184，rs1042098，rs27072)，此外我們根據文獻回顧，再挑選 4 個可能與 ADHD 有相關的 SNP (rs6350，rs403636，rs463379，rs6347) 進行基因型鑑定。

所有 SNP 都是使用 matrix-assisted laser desorption/ionization time of flight

mass spectrometry (MALDI-TOF MS) 進行基因型鑑定，使用 SpectroDESIGNER 軟體設計位於 SNP 側區的引子和探針，並以 GeneAmp 9700 反應熱循環儀進行 4 複合聚合酶鏈鎖反應 (PCR) 放大包含 SNP 位置的 DNA 片段 (100-300 bp)，依廠商提供之說明，反應條件設為 95℃、15 分鐘後，變性 95℃、20 秒，黏合 56℃、30 秒，延伸 72℃、1 分鐘，共進行 45 次循環，最後以 72℃、3 分鐘完成反應。為中和未反應之三磷酸去氧核苷酸 (dNTP)，於 PCR 反應混合液中加入蝦鹼性磷酸酶 (shrimp alkaline phosphatase，SAP)，並在 37℃反應 20 分鐘，將未反應之 dNTP 轉化為雙磷酸去氧核苷酸 (dNTP)。之後將反應混合液靜置 85℃、5 分鐘，去除 SAP 活性。接著進行引子延伸，加入探針、Thermo Sequenase 與適當的三磷酸雙去氧核苷酸 (ddNTP) / dNTP 混合物，變性 94℃、5 秒，黏合 52℃、5 秒，延伸 72℃、5 秒，共進行 55 次循環，最後使用 MALDI-TOF，依質量區分不同的延伸產物。3' VNTR 則依照過去的文獻的實驗方式 (Genro et al., 2008)，以 PCR 加以鑑定。

2.4.1.3. 統計分析

基因型的資料使用 Haploview 軟體進行 Hardy-Weinberg equilibrium (HWE) 檢驗，同時也以 Haploview 軟體進行單套體區間的評估。我們使用 Family-Based Association Test (FBAT) 軟體分析基因型與 ADHD 之間相關性的分析，模式預設為至少要有 10 個 informative 家庭才會進行分析，Alpha 值設定在 0.05，另外我們使用 Bonferroni 校正以減少多重比較所產生的誤差。另外我們也使用內建於 FBAT 的 Haplotype-Based Association Test (HBAT) 來進行單套體相關性分析，並以 permutation 校正多重比較所產生的誤差。

2.4.2. *DAT1* 基因與執行功能障礙之相關性

2.4.2.1. 受試者

本研究延續了我們先前的遺傳基因研究，收集了 382 位 7 到 18 歲的青少年 ADHD 患者，其中 86.1%為男性，平均年齡為 10.5±2.6 歲，母親與個案均分別接受精神科診斷性會談工具 K-SADS-E 的評估，以確立其診斷。在 382 位 ADHD 患者中，有 67.3%診斷為混合亞型，27.0%為注意力不足亞型，5.7%為過動衝動亞型。同時我們也收集了患者的家族 DNA 樣本，其中 164 個家庭是一位初始患者 (proband)、一位手足、以及父母雙親，15 個家庭是一位初始患者、兩位手足、以及父母雙親，144 家庭是一位初始患者、以及父母雙親，17 個家庭是一位初始患者、一位手足、以及一位父親或母親，42 個家庭是一位初始患者、以及一位父親或母親，最後總樣本數為 1298 人，在 211 位手足中 43.6%為男性，平均年齡為 11.4±3.9 歲，其中 57 位手足符合 ADHD 診斷，而 28.1%診斷為混合亞型，50.9%為注意力不足亞型，21%為過動衝動亞型。

2.4.2.2. 神經心理測驗：CABTAB

我們選用 CANTAB 的 IED、SSP、SWM、SOC 評估受試者的執行功能，關於執行功能測驗請見 2.1.1.2。

2.4.2.3. 選取 SNP 與基因型鑑定

我們選取了 15 個 DAT1 的基因標記，選取的方法與基因型鑑定請見 2.4.1.2。

2.4.2.4. 統計分析

基因型的資料使用 Haploview 軟體進行 Hardy-Weinberg equilibrium (HWE) 檢驗，同時也以 Haploview 軟體進行單套體區間的評估。我們使用 Family-Based Association Test (FBAT) 軟體分析基因型與執行功能之間相關性的分析，模式預設為至少要有 10 個 informative 家庭才會進行分析，Alpha 值設定在 0.05，另外我們使用 Bonferroni 校正以減少多重比較所產生的誤差。另外我們也使用內建於

FBAT 的 Haplotype-Based Association Test (HBAT) 來進行單套體相關性分析，並以 permutation 校正多重比較所產生的誤差。

3. 結果 (Results)

3.1 注意力不足過動症的神經認知功能障礙

3.1.1 神經認知功能障礙

53 位兒童時期被診斷為 ADHD 的患者中，有 19 位 (35.8%) 到了青少年時期符合注意力不足亞型，18 位 (34.0%) 符合混合亞型，6 位 (11.3%) 符合過動衝動亞型，但有 10 位 (18.9%) 已經不符合 ADHD 的診斷。在精神科疾病的共病方面，對立反抗性疾患最多 (oppositional defiant disorder，ODD) (73.6%)，其次為焦慮疾患 (41.5%)，與對照組相比，ADHD 組較易有對立反抗性疾患、行為規範疾患 (conduct disorder，CD)、雙極性情感精神病、畏懼症、以及睡眠障礙 (表 2)。

表 3 總結了受試者執行功能測驗的表現，與對照組相比較，在 SSP 方面，ADHD 組有較差的使用錯誤數 (total usage errors)，但在總錯誤數 (total errors) 和空間記憶廣度 (spatial span length) 則沒有顯著差異；在 IED 方面，ADHD 組有較高的完成測驗所嘗試次數 (trials to complete the stages)，但在完成測驗的最高數目 (maximum number of stages completed)、前向度外轉換錯誤數 (pre-ED shift errors)、和向度外轉換錯誤數 (ED shift errors) 則沒有顯著差異；在 SWM 方面，ADHD 組有較差的總錯誤數 (total number of errors)，特別是在 6-box 和 8-box 的問題上，但在策略使用上 (strategy utilization) 則沒有顯著差異，進一步分析則顯示，當 SWM 測驗難度增加時，ADHD 組與對照組的差異會明顯增加；在 SOC 方面，ADHD 組有較差的以最少移動解決問題數 (problems solved in the minimum number of moves)、總移動數 (total moves)、初始思考時間 (initial thinking time)、和持續思考時間 (subsequent thinking time)，進一步分析則顯示，當 SOC 測驗難度增加時，ADHD 組與對照組的差異會明顯增加。

3.1.2 神經認知內表現型

　　表 4 總結了三組受試者在基本資料的比較，其中在性別、父母的教育程度、以及母親的年齡方面三組有差異，表 5 則呈現三組在精神病理的比較，與對照組相比，ADHD 患者有較多的 ODD、CD、抽搐症、憂鬱疾患、以及焦慮疾患，與未發病手足相比，ADHD 患者有較多的 ODD 和 CD；與對照組相比，未發病手足有較多的焦慮疾患。

　　表 6 總結了受試者執行功能測驗的表現，與對照組相比較，在數字廣度方面，ADHD 組有較差的順序與逆序表現，而未發病手足則有較差的逆序表現；在 IED 方面，ADHD 患者與未發病手足有較差的向度外轉換錯誤數 (EDS errors)、和總錯誤數 (total raw and adjusted errors)；在 SSP 方面，ADHD 患者有較差的成功回憶廣度 (span sequences successfully recalled) 和總使用錯誤數 (total usage errors)，而未發病手足有較差的成功回憶廣度；在 SWM 方面，ADHD 患者和未發病手足有較差的策略使用上 (strategy utilization)和總錯誤數 (total errors in searching the box)，進一步分析則顯示，當 SWM 測驗難度增加時，ADHD 患者以及未發病手足與對照組的差異會明顯增加 (圖 1a)；在 SOC 方面，ADHD 患者和未發病手足有較差的以最少移動解決問題數 (problems in the minimum number of moves)、平均移動數 (mean moves)、和初始思考時間 (initial thinking time)，進一步分析則顯示，當 SOC 測驗難度增加時，ADHD 患者以及未發病手足與對照組的差異會明顯增加 (圖 1b)。我們檢驗三組之間在執行功能方面是否有線性趨勢，結果發現對照組、未發病手足、和 ADHD 患者，在以下的測驗表現都有明顯的線性趨勢，包括數字廣度、IED 的總錯誤數 (total errors)、SSP 的空間記憶廣度 (spatial length) 和總使用錯誤數 (total usage errors)、SWM 的總錯誤數 (total errors) 和使用策略 (strategy utilization)、SOC 的以最少移動解決問題數 (problems solved in minimum moves)、總移動數 (total moves)、和平均初始思考時間 (mean initial thinking time)。

表 7 總結了受試者視覺記憶測驗的表現，與對照組相比較，在 DMS 方面，ADHD 患者有較差的 B"、同時情境下正確反應的平均潛在反應時間 (mean latency of correct responses in simultaneous tasks)、同時情境下的正確反應數 (number of correct responses in simultaneous tasks)、以及延遲情境下的正確反應數 (number of correct responses in all delay tasks)，而未發病手足有較差的錯誤反應可能性 (probability of an error following a correct response and following an error response)、和延遲情境下的正確反應數 (number of correct responses in total and all delays)，進一步分析則顯示，當 DMS 測驗難度增加時，ADHD 患者以及未發病手足與對照組的差異會明顯增加 (圖 2)；在 SRM 方面，ADHD 患者有較差的正確反應百分比 (percent of correct responses)，而未發病手足的表現則介於中間；在 PAL 方面，ADHD 患者有較差的總錯誤數 (adjusted total errors)、成功的嘗試總數 (total trials to success)、和第一次嘗試的記憶分數（first trial memory scores)，而未發病手足的表現則介於中間；在 PRM 方面，我們沒有發現明顯的差異。我們檢驗三組之間在視覺記憶方面是否有線性趨勢，結果發現對照組、未發病手足、和 ADHD 患者，在大部分的測驗表現都有明顯的線性趨勢，除了 DMS 的延遲情境下的平均潛在反應時間 (mean latency in all delays)、以及 SRM 的正確反應百分比 (percentage of correct responses)。

3.2 注意力不足過動症的內表現型與藥物治療

表 8 總結了受試者的基本資料，平均 IQ 為 105.37 ±13.55，在服用 atomoxetine 七天之後，受試者服用的平均劑量為 1.20±0.07 mg/Kg，在服用 atomoxetine 十二週之後，受試者的體重、收縮壓、舒張壓、以及脈搏速率並無明顯差異。

表 9 顯示了在使用 atomoxetine 之後 ADHD 症狀的改變，臨床醫師所評估的 CGI-ADHD-S 分數在 4 週時由 5.57 降為 3.43，在 12 週時則降為 2.83；在父母所評估的 CPRS-R: S 和 SNAP-IV-Parent forms，在 4 週 (Cohen d, -0.51~-0.90) 和 12

(Cohen *d*, -0.80~-1.15) 週都有明顯的改善。

　　表 10 顯示了在使用 atomoxetine 之後 ADHD 患者執行功能表現的改變，在 IED 方面，4 週時前向度外轉換錯誤數 (pre-EDS errors)、向度外轉換錯誤數 (EDS errors)、和總嘗試數與總錯誤數 (adjusted total trials and errors) 有明顯進步，12 週時向度外轉換錯誤數 (EDS errors)、總嘗試數與總錯誤數 (adjusted total errors and trials)、和完成的階段數 (completed stages) 有明顯進步；在 RVIP 方面，4 週和 12 週時總正確反應數 (total hits)、總漏失反應數 (total misses)、正確反應可能性 (probability of hits)、正確拒絕總數 (total correct rejections)、對錯誤的敏感度 (sensitivity to errors)、和正確反應的平均潛在時間 (mean latency to respond correctly) 等都有明顯進步；在 SSP 方面，4 週時總使用錯誤數 (total usage errors) 有明顯進步，12 週時成功回憶廣度 (span sequences successfully recalled)、和總使用錯誤數 (total usage errors) 有明顯進步；在 SWM 方面，12 週時策略使用 (strategy utilization) 和總錯誤數 (total errors) 有明顯進步，並且總錯誤數 (total errors) 的困難度與三次回診追蹤之間具有交互作用；在 SOC 方面，4 週時初始和持續思考時間 (initial and subsequent thinking time) 有明顯進步，12 週時總移動數 (total moves)、以最少移動解決問題數 (problems solved in the minimum number of moves)、和初始和持續思考時間 (initial and subsequent thinking time) 有明顯進步，並且平均移動數 (mean moves) 與持續思考時間 (subsequent thinking time) 的困難度與三次回診追蹤之間具有交互作用。

　　表 11 顯示了在使用 atomoxetine 之後 ADHD 患者視覺記憶表現的改變，在 PRM 方面，4 週時正確反應的平均潛在時間 (mean latency of correct responses)、和總正確反應數 (total correct responses) 有明顯進步，12 週時正確反應的平均潛在時間 (mean latency of correct responses) 有明顯進步；在 SRM 方面，12 週時正確反應的平均潛在時間 (mean latency of correct responses) 有明顯進步 (圖 3)。

3.3 注意力不足過動症的執行功能障礙與神經影像學

圖 4 顯示了尾核–背外側前額葉 (caudate nucleus–DLPFC)、尾核–內側前額葉 (caudate nucleus–MPFC)、尾核–眼窩額葉 (caudate nucleus–OFC)、以及尾核–腹外側前額葉 (caudate nucleus–VLPFC) 等四條額葉紋狀體神經路徑。表 12 顯示了 ADHD 組與對照組在基本資料方面的描述。圖 5 顯示與對照組相比，ADHD 患者在兩側的額葉紋狀體神經路徑之 GFA 較低，若比較左右兩側的 GFA，則發現 ADHD 患者在內側前額葉與背外側前額葉兩條神經路徑失去左側化的現象。表 13 顯示與對照組相比，ADHD 患者在 IED、RVP、SWM、及 SOC 等各方面的執行功能表現均較差。

表 14 顯示在經過多重線性迴歸分析之後，我們發現注意力不足症狀與右側的眼窩額葉之 GFA 有顯著相關，而過動衝動症狀與左側背外側前額葉的和右側內側前額葉之 GFA 有顯著相關。表 15 顯示 ADHD 患者的 IED 總錯誤數和總嘗試數與左側眼窩額葉和腹外側前額葉之 GFA 有顯著相關；RVP 錯誤反應可能性 (probability of false alarm) 和 B"與左側眼窩額葉之 GFA 有顯著相關；SWM 總錯誤數與左側眼窩額葉之 GFA 有顯著相關；SOC 以最少移動解決問題數和平均初始思考時間與左右兩側背外側前額葉之 GFA 有顯著相關；SOC 平均持續思考時間與左側背外側前額葉之 GFA 有顯著相關。

3.4 注意力不足過動症的基因遺傳學

3.4.1 *DAT1* 基因與注意力不足過動症的相關性研究

在 19 個 DAT1 基因標記中有 4 個的基因鑑定成功率低於 70% (rs6350、rs10052016、rs6347、rs11133767)，其餘的 15 個標記都有符合 Hardy-Weinberg 平衡，表 16 呈現了這 15 個基因標記的次要對偶基因頻率 (minor allele frequency，MAF) 以及在 DAT1 基因上的位置。圖 6 顯示了這 15 個基因標記的 LD 結構，其中包含了 3 個單套體區間，第一個區間大小為 19kb，位於第二、四、

六個內顯子，第二個區間大小為 3kb，位於第八、十一個內顯子，第三個區間大小為 953bp，位於 3′UTR。

在基因與 ADHD 診斷的相關性分析方面，並無任何標記有達到統計顯著意義；若區分為不同的亞型，我們發現只有一個 SNP rs37020 G allele ($P = 0.038$) 與混合亞型有顯著相關，但經過多重比較的校正之後則相關性消失；有一個 SNP rs429699 T allele ($P = 0.017$) 與注意力不足亞型有顯著相關，但經過多重比較的校正之後則相關性消失 (表 17)。

在單套體分析方面，第二個單套體區間 rs27048 (C) /rs429699 (T) 與 ADHD 有顯著相關，但經過 permutation 校正之後則相關性消失；若區分為不同的亞型，我們發現第一個單套體區間 rs403636 (G) /rs463379 (C) /rs393795 (C) /rs37020 (G) 與混合亞型有顯著相關，但經過 permutation 校正之後則相關性消失；第二個單套體區間 rs27048 (C) /rs429699 (T) 與注意力不足亞型有顯著相關，經過 permutation 校正之後相關性仍然持續存在 (表 18)。

3.4.2 *DAT1* 基因與執行功能障礙之相關性

圖 7 顯示了這 15 個基因標記的 LD 結構，其中包含了 3 個單套體區間，第一個區間大小為 19kb，位於第二、四、六個內顯子，第二個區間大小為 3kb，位於第八、十一個內顯子，第三個區間大小為 660bp，位於 3′UTR。在基因與 ADHD 診斷的相關性分析方面，並無任何標記有達到統計顯著意義 (表 19)；在單套體分析方面，這些單套體區間與 ADHD 之間並無顯著相關性。

在執行功能的分析方面，我們發現 rs2937639 與 SWM 組內錯誤 (within errors) ($P = 0.049$) 有相關性，rs2617605 與 SWM 組內錯誤 (within errors) ($P = 0.004$)、SWM 組內錯誤 (within errors) 8 boxes ($P = 0.007$)、SWM 雙重錯誤 (double errors) ($P = 0.002$)、以及 SWM 雙重錯誤 (double errors) 8 boxes ($P = 0.009$) 有相關性，rs403636 與 SWM 雙重錯誤 (double errors) ($P = 0.024$) 有相關性，

rs37020 與 SWM 雙重錯誤 (double errors) ($P = 0.004$)、以及 SWM 雙重錯誤 (double errors) 8 boxes ($P = 0.033$) 有相關性 (表 20)。

在單套體分析方面，第一個單套體 rs403636 (G) /rs463379 (C) /rs393795 (C) /rs37020 (G) 與 SWM 組內錯誤 (within errors) ($P = 0.0005$)、SWM 組內錯誤 (within errors) 8 boxes ($P = 0.001$)、SWM double errors ($P = 0.0007$)、以及 SWM 雙重錯誤 (double errors) 8 boxes ($P = 0.002$) 有相關性 (表 21)，經過 permutation 校正之後，rs403636 (G) /rs463379 (C) /rs393795 (C) /rs37020 (G) 與 SWM 組內錯誤 (within errors) (2-sided $P = 0.0003$; the smallest observed $P = 0.001$)、SWM 組內錯誤 (within errors) 8 boxes (2-sided $P = 0.0003$; the smallest observed $P = 0.002$)、SWM 雙重錯誤 (double errors) (2-sided $P = 0.0004$; the smallest observed $P = 0.001$)、SWM 雙重錯誤 (double errors) 8 boxes (2-sided $P = 0.0007$; the smallest observed $P = 0.004$) 仍呈現顯著相關。至於 SSP、IED、和 SOC，並無和 *DAT1* 上的基因標記呈現相關性。
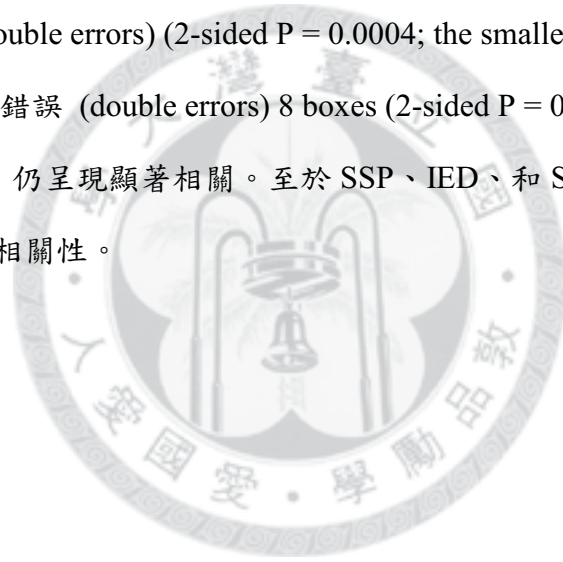
4. 討論 (Discussion)

總結以上的研究結果，我們是第一個研究團隊發現華人青少年 ADHD 患者合併有執行功能障礙 (Gau et al., 2009)，其中包括了短期空間記憶、空間工作記憶、注意力轉換、以及空間計畫能力等方面，特別是當測驗的難度增加時，這些障礙會變得更明顯，即使在控制了智商、藥物的使用、以及精神科疾病的共病之後，ADHD 患者的執行功能障礙仍然存在。除了 ADHD 患者會合併執行功能障礙之外，我們也進一步發現，ADHD 患者之未發病手足雖然臨床上並未符合 ADHD 的診斷，但與健康受試者相比，其執行功能與視覺記憶仍然呈現許多明顯的障礙 (Gau & Shang, 2010a; Shang & Gau, 2011)，包括了以數字廣度的逆序作業 (backward) 所測量的語言工作記憶 (verbal working memory)，和以 CANTAB 所測量的空間短期記憶、空間工作記憶、空間計畫、反應抑制、延遲樣本配對、以及空間辨認記憶等能力，我們的發現證實了執行功能與視覺記憶障礙在 ADHD 患者的家族遺傳性，而 ADHD 患者未發病手足雖然並未罹患 ADHD 的臨床診斷，但仍然有與 ADHD 患者相類似的執行功能與視覺記憶障礙，因此可以支持神經心理功能是比外在症狀更接近 ADHD 致病基因的生物標記 (D. I. Slaats-Willemse et al., 2007)，因此我們的研究證實了執行功能與視覺記憶障礙可以做為 ADHD 的內表現型。

在 ADHD 的內表現型與藥物治療方面，我們是世界上第一個在兒童 ADHD 患者同時研究 atomoxetine 對於執行功能和視覺記憶障礙的治療效果 (Gau & Shang, 2010b; Shang & Gau, 2012)，與過去成人患者的研究相比較，我們的研究收集了較多的樣本、有較長的追蹤期間、並且有較多的追蹤次數 (S. R. Chamberlain et al., 2007; S. V. Faraone et al., 2005; T. Spencer et al., 1998)，我們研究的主要發現為 atomoxetine 可以改善兒童 ADHD 患者的執行功能與視覺記憶障礙，包含持續注意力 (RVIP)、控制能力 (RVIP)、注意力轉換作業 (IED)、空間

短期記憶 (SSP)、空間工作記憶 (SWM)、空間計畫與問題解決能力 (SOC) 、型

態辨認記憶 (PRM)、以及空間辨認記憶 (SRM) 等，此外，空間計畫與問題解決

能力的改善程度和 atomoxetine 使用的持續時間與測驗的難度有關。因此我們的

研究結果與過去的動物 (Blondeau & Dellu-Hagedorn, 2007; L. A. Newman et al.,

2008; Robinson et al., 2008) 和成人 (S. R. Chamberlain et al., 2007; S. V. Faraone

et al., 2005; T. Spencer et al., 1998) 研究一致，atomoxetine 確實可以改善 ADHD

患者的執行功能障礙，我們也是世界上第一個研究發現 atomoxetine 對於 ADHD

患者的視覺記憶有改善的療效；此外，我們也與過去研究 (S. V. Faraone et al.,

2005; T. Spencer et al., 1998) 一致地發現，長期服用 atomoxetine 並不會對 ADHD

患者的神經心理功能造成負面影響；最後，我們也發現使用家長評估與臨床醫師

評估的工具，皆顯示 atomoxetine 能有效地改善兒童 ADHD 患者的行為症狀

(Bangs et al., 2008; Caballero & Nahata, 2003; Gau et al., 2007)。

　　在 ADHD 的執行功能障礙與神經影像學方面，藉著 tractography-based 的分

析、完整地評估受試者的臨床症狀和執行功能、以及配對的病例對照研究設計，

我們發現兒童 ADHD 患者在兩側額葉紋狀體的神經路徑均有細微結構完整性的

缺損，並且臨床症狀及執行功能障礙與額葉紋狀體神經路徑的缺損呈現相關，特

別是在 orbitofrontal 與 ventrolateral 的神經纖維其相關性更加顯著 (Shang et al.,

2012)，因此我們的研究結果支持了額葉紋狀體神經路徑完整性的缺損，是導致

ADHD 的臨床症狀和執行功能障礙的可能原因。

　　在 ADHD 的基因遺傳學方面，我們的研究針對 DAT1 上的 15 個基因變異，

發現在 DAT1 基因上有三個單套體區間，並且單套體 rs27048 (C) /rs429699 (T)

與注意力不足亞型之間有顯著的相關性，我們的研究是第一個在華人族群中探討

DAT1 基因的 LD 結構 (Shang et al., 2011)，而我們的結果也證實了 DAT1 基因在

ADHD 的致病機轉上扮演重要的角色。我們進一步探索 DAT1 基因與 ADHD 的

執行功能障礙之間的關係，結果發現單套體 rs403636 (G) /rs463379 (C) /rs393795

(C) /rs37020 (G)與空間工作記憶之間有顯著相關性，因此我們的結果支持 DAT1

基因變異可能會導致 ADHD 的特定執行功能障礙，以下分別就這六個研究做詳

盡的討論。

4.1 注意力不足過動症的神經認知功能障礙

4.1.1. 神經認知功能障礙

4.1.1.1. 討論

首先我們發現，這些兒童時期被診斷為 ADHD 的患者，到了青少年期仍然

有超過五分之四以上符合 ADHD 的臨床診斷，雖然 ADHD 的過動與衝動症狀會

隨著年齡的增長而嚴重度逐漸下降 (Biederman et al., 2000)，我們的研究結果顯

示即使到了青少年時期，大多數的患者其整體症狀仍然符合 ADHD 的診斷

(Wilens et al., 2002)。

使用 CANTAB 為工具來做完整的神經心理功能評估，我們發現 ADHD 患者

有明顯的執行功能障礙 (*d*=0.4~0.6)，這項結果和過去國外的研究結果是一致的

(Willcutt et al., 2005)，並且我們的結果不支持 Barkely 等人的假說認為 ADHD 只

是單一功能障礙的疾病 (Barkley, 1997)，反而我們發現 ADHD 會同時合併許多

層面的執行功能障礙，這和過去西方使用 CANTAB 評估兒童 ADHD 患者的研究

結果相似，也就是 ADHD 會合併短期空間記憶 (Pennington & Ozonoff, 1996;

Rhodes et al., 2005)、空間工作記憶 (Rhodes et al., 2005)、注意力轉換 (Kempton et

al., 1999)、以及空間計畫能力 (Rhodes et al., 2005) 等方面空間執行功能的障

礙。與過去研究相似 (Martinussen et al., 2005)，我們的結果發現 ADHD 患者並

未有明顯口語工作記憶的障礙，因此空間的執行功能測驗更可以偵測出 ADHD

患者的神經認知功能障礙。

我們發現當空間工作記憶與空間計畫測驗的難度增加時，青少年 ADHD 患

者的執行功能障礙會變得更加明顯，這表示當學校作業或考試的困難度提高時，

ADHD 患者會更容易出現不佳的表現。在成人的研究也顯示 (Young et al.,

2007)，當測驗的難度增加時，健康受試者的思考解決問題的時間會增加，但 ADHD 患者的思考時間並未有任何改變。因此綜合上述研究成果，當作業難度增加時，ADHD 患者在思考解決問題的衝動性也增加，但最後的表現則變差。

雖然執行功能障礙是 ADHD 患者在接受神經心理測驗時的表現，但過去研究顯示，這些障礙會影響實際生活的功能，例如 Gropper 等人發現 ADHD 的學生患者，其工作記憶的能力和學業成績具有明顯相關性 (Gropper & Tannock, 2009)，Stavro 等人則發現較差的執行功能和較差的適應功能有相關性 (Stavro et al., 2007)，Barkley 等人則發現在控制了 ADHD 症狀嚴重程度之後，執行功能障礙和交通意外事故之間有明顯的相關性 (Barkley et al., 2002)，由於執行功能障礙會影響 ADHD 患者的組織規畫能力，可能因此造成患者無法適當地完成日常生活的工作和作業，因此執行功能障礙可以反應 ADHD 患者的實際功能障礙。

雖然過去研究顯示 methylphenidate 可以改善 ADHD 患者的執行功能障礙 (Elliott et al., 1997; Kempton et al., 1999)，但我們的研究卻發現 methylphenidate 的使用和較差的執行功能障礙有相關性，這可能是由於在我們的研究中藥物的治療並非隨機分配，因此一些干擾因素，如 ADHD 的症狀嚴重度和精神疾病的共病等，都會對於病人是否使用藥物治療產生影響 (Epstein et al., 2006; Kessler et al., 2005)，因此藥物治療對於 ADHD 患者的執行功能障礙的效應如何，仍有待後續前瞻性的研究加以探討。

4.1.1.2. 研究限制及優點

本研究有以下幾項研究限制，第一，雖然比起過去的研究來說我們的青少年 ADHD 患者樣本數不算少，但若能收集更多的樣本，將有助於完整探索 ADHD 的異質性和執行功能障礙之間的關係；第二，我們的研究所收集的是門診轉介的 ADHD 患者，因此研究結果是否能類推至一般的社區青少年 ADHD 患者仍有待進一步證明，但是過去的 meta-analysis 顯示 (Willcutt et al., 2005)，社區研究樣本的執行功能障礙其效應值 (*Cohen's d* = 0.49 ± 0.06) 只略低於門診轉介樣本的效

應值 (*Cohen's d* = 0.56 ± 0.04) ，因此可以推論，執行功能障礙並不限於門診轉介的 ADHD 患者才會出現。

除了上述的限制之外，本研究也有幾項優點，第一，我們使用配對的病例對照研究，因此可以有效避免性別、年齡、社經地位、以及智商等干擾因子對於執行功能表現的影響；第二，我們使用標準化的神經心理測驗 CANTAB，可以完整並且準確地評估受試者的執行功能；第三，我們對於青少年受試者和其母親進行完整的精神科評估，這一個族群在西方的研究較少被探討，因此我們的研究結果可以證實青少年 ADHD 患者確實合併有執行功能障礙的問題。

總結來說，雖然 ADHD 的症狀會隨年紀增加而逐漸改善，但是執行功能的障礙仍然會持續到青少年時期，而執行功能障礙會進一步影響青少年的課業和社會人際功能 (Biederman et al., 2004)，因此未來對於 ADHD 患者除了評估其臨床症狀之外，也應考慮對其執行功能進行完整的評估，以便針對青少年 ADHD 患者的課業和社會人際功能予以適當的預防處置 (Biederman et al., 2007)。此外我們進一步發現，當空間工作記憶與空間計畫等作業的難度增加時，ADHD 患者的表現會明顯下降，這個發現可以解釋 ADHD 患者在面對需要專心思考的家庭作業時會有逃避的反應，因此當分派複雜的作業給 ADHD 患者時，我們建議應該也同時提供適當的協助，讓患者能有效地完成作業。除了執行功能之外，未來應針對 ADHD 患者的其他神經心理功能加以評估，以便對於 ADHD 的病理生理機轉的異質性有更全面性的了解。

4.1.2. 神經認知內表現型

4.1.2.1. 討論

我們是第一個研究團隊在大規模的 ADHD 患者和其未發病的手足，以 CANTAB 和數字廣度為工具評估受試者完整的神經心理功能，包含了低階的 (空間廣度和數字廣度) 與高階的 (語言和空間工作記憶) 執行功能測驗。而我們的

研究結果證實了這些執行功能障礙確實可以做為 ADHD 的內表現型，因為這點符合了 Doyle 等學者所提出來內表現型的重要條件 (Doyle et al., 2005)，即這些執行功能障礙不但與 ADHD 同時發生，而且也出現在 ADHD 家族中未發病的親屬身上。雖然過去有些研究並未發現 ADHD 患者之未發病親屬有神經心理功能的障礙 (Asarnow et al., 2002)，但我們的研究證實 CANTAB 有很好的敏感性，因而適用於偵測 ADHD 患者之未發病手足潛在的執行功能障礙。由於內表現型會比行為症狀的外在表現型更靠近 ADHD 的致病基因，因此未來進一步探索執行功能障礙與基因之間的關聯性，將有助於探索 ADHD 的病因 (Nigg et al., 2004; L. J. Seidman et al., 2000; D. Slaats-Willemse et al., 2005; D. I. Slaats-Willemse et al., 2007)。

我們先前的研究發現青少年 ADHD 患者的執行功能障礙，會隨著測驗的難度增加而變得更加明顯 (Gau et al., 2009)，而我們在這個更大規模的內表現型研究中不但再次證實了這個結果，而且也是第一個團隊發現 ADHD 患者之未發病手足，其執行功能障礙會隨著測驗難度增加而變得更明顯。雖然過去的研究已發現某些個別的執行功能障礙，例如反應抑制能力 (D. Slaats-Willemse et al., 2003)，可以作為 ADHD 的內表現型，但只使用個別單獨的測驗來評估患者與未發病親屬的執行功能，有可能會導致不同的研究結果之間出現很大的差異性，相對地，我們的研究結果顯示，不是只有某個執行功能可以作為 ADHD 的內表現型，而是許多的執行功能障礙均會伴隨著 ADHD 的家族遺傳性，因此使用完整的測驗工具如 CANTAB，可以對 ADHD 患者與未發病手足的執行功能提供最多的訊息。

在我們的研究中 ADHD 患者之未發病手足的執行功能表現介於 ADHD 患者和健康受試者之間，此外，我們也發現在 ADHD 患者、未發病手足、以及健康受試者三組之間的執行功能表現有顯著的線性關係，包括數字廣度測驗的語言工作記憶、注意力轉換作業的錯誤率、空間短期記憶廣度與錯誤率、空間工作記憶的總錯誤率、以及空間計畫的問題解決能力等，這些結果顯示 ADHD 患者的執

行功能障礙可能是一個帶著基因遺傳的認知行為表現型中的極端 (the extreme of a cognitive-behavioral phenotype with genetic susceptibility) (D. Slaats-Willemse et al., 2003)。

至於精神科的共病方面，過去研究顯示合併有對立反抗性疾患和行為規範障礙疾患的 ADHD 患者，其執行功能障礙較嚴重 (Oosterlaan et al., 2005)，雖然我們的研究顯示 ADHD 患者比未發病的手足有更多的對立反抗性疾患和行為規範障礙疾患，但經過控制精神科共病的因素之後，ADHD 患者和未發病手足均仍然合併有顯著的執行功能障礙，因此精神科共病並非導致 ADHD 患者和未發病手足之執行功能障礙的主要原因，這個發現與過去西方的研究結果相似 (L. J. Seidman et al., 1997; Willcutt et al., 2005)。

除了上述所提到的內表現型之外，我們的研究也發現 ADHD 患者之未發病手足在某些執行功能測驗的表現並無明顯異常，包括 SSP 的 total usage errors，以及 SOC 的 problems solved in 5-move tasks，但 ADHD 患者在這兩個項目上則有明顯障礙，代表這兩個執行功能障礙並不適合作為 ADHD 的內表現型，可能這些障礙是伴隨著 ADHD 疾病本身，或者是由跟家族遺傳不相關的某些因素所造成的 (S. P. H. D. Durston et al., 2004)。

除了上述的執行功能障礙之外，我們也進一步使用 CANTAB 為工具探索視覺記憶是否為 ADHD 的內表現型，在單變項分析中，我們發現 ADHD 患者之未發病手足也有延遲樣本配對 (DMS) 的障礙，而多變項的分析顯示，在 DMS 的錯誤率 (an error following a correct response and following an error response) 以及空間辨認記憶 (SRM) 的正確率 (percent of correct responses) 等方面，這些未發病手足的表現介於 ADHD 患者和健康對照組之間。上述的研究結果顯示了由 DMS 和 SRM 所測量的視覺記憶可以作為 ADHD 的內表現型，因為它們符合了 Doyle 等學者所提出來的條件 (Doyle et al., 2005)，即這些視覺記憶障礙不但與 ADHD 同時發生，而且也出現在 ADHD 家族中未發病的親屬身上，因此我們是世界上第一個研究團隊證實了視覺記憶可以作為 ADHD 的內表現型。

我們的研究結果與過去西方的研究結果相似，發現 ADHD 患者在視覺記憶測驗上有明顯的障礙，包括了空間辨認記憶 (SRM) (Kempton et al., 1999) 、延遲樣本配對 (DMS) (Barnett et al., 2009) 、形態辨認記憶 (PRM) (S. M. Rhodes et al., 2004) 、以及配對相關學習 (PAL) (H. T. Chang et al., 1999) 等方面，此外我們也進一步發現，當 DMS 延遲的時間變長時，亦即測驗難度增加時，ADHD 患者的視覺記憶障礙會變得更加明顯，這可能代表視覺記憶障礙反應了 ADHD 患者在記憶的保留 (retention) 或回憶 (recall) 等方面的困難。

　　進一步分析，我們發現 ADHD 患者在 DMS 的同時情境與延遲情境都有明顯的障礙，雖然 Kempton 等人在一個樣本數較小 (n = 30) 的研究中沒有發現 ADHD 患者有 simultaneous condition 的障礙 (Kempton et al., 1999)，但後來 Rhodes 等人在一項較大規模 (n = 75) 的研究中則與我們一樣，發現 ADHD 患者在 simultaneous condition 也有明顯障礙 (S. M. Rhodes et al., 2004)。當受試者在進行 DMS 測驗的 simultaneous condition 時，必須具備良好的專注力以分辨不同空間刺激之間的微小差異 (Moody et al., 1998)，我們的研究結果發現 ADHD 患者的視覺記憶障礙與其記憶力和專注力困難均有相關 (Nigg, 2005)。

　　與 ADHD 患者相似，當 DMS 測驗難度增加時，未發病手足的視覺記憶障礙會變得更加明顯，過去研究發現，DMS 測驗和腦部特定部位的功能有關，特別是顳葉、杏仁核、以及海馬迴 (Owen et al., 1995)，而過去的腦部影像學研究已證實顳葉 (Wolosin et al., 2009)、杏仁核 (Lopez-Larson et al., 2009)、以及海馬迴 (Plessen et al., 2006) 等部位的異常在 ADHD 的病理生理機轉上扮演著十分重要的角色，此外 Durston 等學者發現，ADHD 患者之未發病手足在腦部顳葉的灰質體積會有減少的趨勢 (S. Durston et al., 2004)，因此未來需要進一步的功能性腦部影像研究，來探索當進行 DMS 測驗時 ADHD 未發病手足的腦部有哪些特定的神經變化。

　　與過去研究相似 (Kempton et al., 1999)，我們並未發現 ADHD 患者在 PRM 的測驗中有較差的反應。PRM 測驗的表現與腦部顳葉的內側部位 (medial

temporal lobe) 的功能有關 (Luciana & Nelson, 1998)，雖然神經影像學研究顯示，ADHD 患者的顳葉內側部位有體積減少 (Brieber et al., 2007) 和局部血液灌流 (Kim et al., 2002) 異常的現象，但神經心理學研究卻發現，在與顳葉內側部位有關的神經心理測驗中，ADHD 患者並未有較差的表現 (Barnett et al., 2005)。最近的動物模式研究顯示，雖然 SHR (spontaneously hypertensive rat) 與 ADHD 患者有相似的行為表現型，但是在與顳葉內側部位有關的神經行為功能檢查中並未出現異常 (Wells et al., 2010)。

此外我們的研究也發現 ADHD 的症狀是否持續並不會影響視覺記憶障礙，因此這表示 ADHD 症狀雖然會隨著患者年紀的增加而逐漸改善，但潛在的視覺記憶障礙仍然會持續至青少年期，所以視覺記憶障礙可以被視為一種特質標記 (trait marker) 而非症狀標記 (state marker) (Biederman et al., 2009)。我們的研究也顯示使用 methylphenidate 與較差的視覺記憶表現有關，並且愈大的年齡才使用 methylphenidate 會伴隨較好的空間辨認記憶，由於 methylphenidate 在我們的研究中並非隨機分配，因此如 ADHD 的症狀嚴重度和精神疾病的共病等干擾因素，都可能對於病人是否使用藥物治療產生影響 (Epstein et al., 2006; Kessler et al., 2005)，因此 methylphenidate 對於 ADHD 患者的視覺記憶障礙的效應如何，仍有待後續前瞻性的研究加以探討。

4.1.2.2. 研究限制及優點

我們的內表現型研究有以下幾項研究限制，第一，雖然本研究的 ADHD 患者在接受神經心理測驗之前必須先停藥 24 小時，但我們並未進行血液或尿液的藥物篩檢，以確定患者是否有依照指示在接受測驗前停止服用藥物，所以我們無法完全排除藥物對於執行功能或視覺記憶可能造成的影響，不過因為大多數臨床上的 ADHD 患者都有接受藥物的治療 (L. J. Seidman et al., 1997)，所以我們的研究結果仍然深具臨床參考價值；第二，我們只有使用數字廣度測驗評估受試者的

語言工作記憶，因此其它語言執行功能的層面是否合適作為 ADHD 的內表現型，則有待後續研究加以探討；第三，在我們的研究中大多數 ADHD 患者為男生，因此仍需要進一步的研究來探索性別因素對於 ADHD 內表現型的影響；第四，由於我們的研究是 sibling design 而非 twin design，因此無法完全排除 ADHD 患者與未發病手足之間共享的環境因子 (shared environmental factors) 對於執行功能和視覺記憶障礙的影響。

除了上述的限制之外，本研究也有幾項優點，第一，我們是第一個研究在華人族群使用標準化的神經心理測驗 CANTAB，以評估 ADHD 患者之未發病手足的執行功能，而 CANTAB 已在過去的研究中證實具備良好的信效度 (Gau et al., 2009; Luciana & Nelson, 1998)；第二，我們收集了大規模的樣本，包含了 ADHD 患者、未發病手足、以及健康對照組，因此我們的研究結果是十分有說服力的；第三，我們對於 ADHD 患者之手足和其母親進行完整的精神科診斷會談，這樣的做法可以對 ADHD 患者之手足作正確的診斷，避免將那些符合 ADHD 診斷的手足納入樣本中。

4.1.2.3. 結論

總結來說，由 CANTAB 與數字廣度測驗所測量的執行功能和視覺記憶障礙可以作為 ADHD 的內表現型，因為這些執行功能和視覺記憶障礙不但會出現在 ADHD 患者身上，同時 ADHD 患者之未發病手足也會出現相類似的執行功能和視覺記憶障礙。在 ADHD 的分子基因研究中使用內表現型可以大幅提升偵測基因變異的檢定力，因此可以更加有效地找出 ADHD 的致病基因，同時也可以使用內表現型來探索 ADHD 腦部的神經病變。在教育方面，對於 ADHD 患者之未發病手足，雖然其行為症狀上並不符合 ADHD 的診斷，但可能由於潛在的執行功能和視覺記憶障礙而影響到這些手足的課業學習，特別是在作業的難度增加時其表現更可能受到影響，因此在進行 ADHD 患者的臨床診療時，也應針對 ADHD

患者之未發病手足給予適當的評估和協助，避免因為他們沒有 ADHD 的臨床診斷而忽略了潛在的執行功能和視覺記憶障礙，並提升其課業學習與人際互動的能力。

4.2 注意力不足過動症的內表現型與藥物治療

4.2.1. 討論

雖然 Spencer 等人曾報告 atomoxetine 並不會對於 ADHD 患者的聽覺注意力 (auditory CPT) 有改善的療效 (T. Spencer et al., 1998)，但我們的研究確實發現 atomoxetine 可以明顯改善 ADHD 患者的視覺注意力 (RVIP)，這項結果與正腎上腺素可以調控注意力的理論是一致的 (J. T. Coull et al., 2004; De Martino et al., 2008)，此外，atomoxetine 可以改善 RVIP 測驗中正確拒絕 (correct rejections) 的比率，代表 atomoxetine 可以降低 ADHD 患者的衝動並提升其抑制能力 (Barton et al., 2005; Robinson et al., 2008)。

雖然在過去成人 ADHD 患者的研究中並未報告 atomoxetine 可以改善注意力轉換能力 (S. R. Chamberlain et al., 2007; T. Spencer et al., 1998)，但我們的研究確實發現 atomoxetine 可以改善兒童 ADHD 患者的注意力轉換能力 (IED)，動物研究的證據顯示正腎上腺素系統可以調節認知的靈活性 (cognitive flexibility)，因為減少前額葉的正腎上腺素濃度會造成實驗動物的注意力轉換作業表現下降 (Lapiz & Morilak, 2006; Tait et al., 2007)，相反地，若增加前額葉的正腎上腺素濃度則可以提升注意力轉換作業的表現 (L. A. Newman et al., 2008)。

雖然在過去成人 ADHD 患者的研究中並未報告 atomoxetine 可以改善空間工作記憶 (S. R. Chamberlain et al., 2007)，但我們的研究確實發現 atomoxetine 可以改善兒童 ADHD 患者的空間工作記憶 (SWM) 和空間短期記憶 (SSP)，動物研究顯示，當實驗動物在進行空間工作記憶測驗時，其前額葉的正腎上腺素濃度會上升 (Rossetti & Carboni, 2005)，這表示正腎上腺素可能參與了空間訊息的主動

維持 (active maintenance)，並進而影響工作記憶的處理程序 (A. F. T. Arnsten & B.-M. Li, 2005)。我們研究的另一個新發現是，空間計畫與問題解決能力 (SOC) 的改善程度和 atomoxetine 使用的持續時間與測驗的難度有關，過去有研究曾經報告 (H. L. Campbell et al., 2008)，健康受試者在進行困難作業的問題解決時，正腎上腺素系統在整個思考流程中扮演重要角色。

除了執行功能障礙之外，我們的研究還有一個獨特的貢獻，就是發現了 atomoxetine 對於 ADHD 患者的視覺記憶障礙有改善的效果。研究結果顯示在經過 12 週的治療之後，atomoxetine 可以顯著縮短 PRM 與 SRM 正確反應的反應時間，但另一方面，我們也發現 atomoxetine 可以加長注意力測驗的反應時間，這些結果表示 atomoxetine 的療效並非單純地用加快或減慢精神動作 (psychomotor) 的速度來解釋，因為在動物研究也發現，atomoxetine 可以縮短 stop-signal 的反應時間，而同時加長 go-signal 的反應時間 (Bari, Eagle, Mar, Robinson, & Robbins, 2009)，因此 atomoxetine 的治療可以讓受試者在接受不同的測驗時，根據不同的認知需求來調整最恰當的反應時間。

過去成人的研究並未發現 atomoxetine 可以改善 ADHD 患者的視覺記憶 (T. Spencer et al., 1998)，但我們的研究發現 atomoxetine 的治療確實可以明顯地提升 ADHD 患者的視覺記憶，這其中的差異可能與以下幾個因素有關，第一是年齡，我們的研究樣本是收集 8 到 16 歲的 ADHD 患者，而 Spencer 等人所收集的樣本是 19 到 60 歲的 ADHD 患者，我們的樣本的年齡明顯較小；第二是測驗工具，我們使用 CANTAB 中兩個測驗 PRM 與 SRM 來評估患者的視覺記憶，而 Spencer 等人則是使用 Rey-Osterrieth Complex Figure 來評估患者的視覺記憶，關於年齡和測驗工具對於 atomoxetine 在視覺記憶方面療效的影響為何，則需要未來進一步的研究加以探討。

從 atomoxetine 對於 ADHD 患者視覺記憶障礙的療效，我們可以推測 atomoxetine 和 methylphenidate 在神經心理學方面不同的藥物作用機轉。我們的研究顯示 atomoxetine 對於 ADHD 患者的 PRM 和 SRM 測驗表現有顯著的改善效

果，雖然過去 Rhodes 等人使用 CANTAB 為測驗工具，並未發現 methylphenidate 對於 ADHD 患者的 PRM 表現有改善的效果 (S. M. Rhodes et al., 2004)，但在動物研究中，Tzavara 等人則發現 atomoxetine 確實可以改善實驗動物的型態辨認 (pattern recognition) 能力 (Tzavara et al., 2006)。此外，Kempton 等人發現中樞神經刺激劑不能改善 ADHD 患者的 SRM 測驗表現 (Kempton et al., 1999)，而這項結果也在另一個特別針對 methylphenidate 的藥物試驗研究中加以證實 (S M. Rhodes et al., 2006)，而在動物研究中，Zhang 等人則發現正腎上腺素確實在空間辨認記憶功能上扮演著重要的角色。由於 atomoxetine 主要是作用在正腎上腺素系統，而 methylphenidate 則是以多巴胺系統為主，綜合上述我們對於 atomoxetine 的研究結果和過去對 methylphenidate 的研究結果 (Kempton et al., 1999; S. M. Rhodes et al., 2004; S M. Rhodes et al., 2006)，或許我們可以推論在視覺記憶的治療效果上，正腎上腺素扮演一個比多巴胺更重要的角色。

在藥物的副作用監測方面，經過了 12 週的治療期間，ADHD 患者並沒有明顯的體重、血壓、或心跳速率的改變，表示 atomoxetine 在台灣兒童族群的長期使用是相對安全的藥物治療，雖然過去有短期的追蹤研究報告指出，體重減輕是 atomoxetine 治療兒童 ADHD 患者最常出現的副作用 (Michelson et al., 2001; Weiss et al., 2005)，但其它的研究也發現，在經過長期的追蹤之後，atomoxetine 對兒童患者的體重並未造成顯著改變 (Gau et al., 2007; T J. Spencer et al., 2005)。至於血壓和心跳速率，雖然我們的研究並未發現 atomoxetine 對於兒童 ADHD 患者有任何影響，但由於 atomoxetine 會作用在正腎上腺素系統，因此對於使用 atomoxetine 的患者仍建議應定期監測其血壓和心跳速率等生命徵象 (S. R. Chamberlain et al., 2007; Kelsey et al., 2004)。

4.2.2. 研究限制及優點

我們的內表現型與藥物治療研究有以下幾項研究限制，第一，過去有些研究

發現 atomoxetine 的療效與患者的性別有相關 (Wehmeier et al., 2012)，但也有研究顯示 atomoxetine 的療效並無性別上的差異 (Cheng et al., 2007; Robison et al., 2008)，雖然我們的研究所收集的樣本數，是目前世界上針對兒童 ADHD 患者的執行功能障礙和 atomoxetine 治療之間關係研究中最多的，但因為我們所收集的樣本都是男生的 ADHD 患者，因此我們的結果是否能類推至女生的患者則有待進一步的研究加以驗證；第二，是否 atomoxetine 對於 ADHD 不同亞型之執行功能障礙有不同的影響，則我們需要收集更多的樣本才會有足夠的檢定力來探索這個問題；第三，我們的研究沒有安慰劑對照組，由於參加研究的患者需要在研究期間接受總共三次的神經心理測驗，因此需要考慮患者可能會因為缺乏新鮮感 (loss of novelty) 或者學習的效應 (learning effect) 而影響他們在測驗中的表現 (Lowe & Rabbitt, 1998)，進而影響了研究結果的判讀，另外受試者的動機高低也會和神經心理測驗的表現有密切相關 (Locke & Braver, 2008)，但由於 CANTAB 測驗表現在我們的研究中有很好的穩定性，因為 10 個健康受試者的一個月再測信度 (one-month test-retest reliability) 並無顯著差異，因此我們認為 ADHD 患者在接受治療之後其 CANTAB 測驗表現非常明顯的改變，主要還是和藥物的作用有關，而非單純只是由時間或其它因素所能解釋；第四，雖然我們的研究顯示 atomoxetine 對於改善 ADHD 患者的執行功能具有明顯效果，但未來仍需要設計功能性神經影像學研究，以進一步探索 atomoxetine 是透過甚麼樣的神經迴路機轉來改善 ADHD 患者的執行功能障礙 (S. R. Chamberlain et al., 2009)。

　　除了上述的限制之外，本研究也有幾項優點，第一，我們是第一個團隊收集大規模的兒童 ADHD 患者，進行完整的神經心理學測驗，以探討 atomoxetine 對執行功能障礙的影響；第二，我們對於患者本身和母親進行臨床與標準的精神科會談評估，可以確認患者 ADHD 診斷的正確性，並且對於 atomoxetine 治療之後行為症狀的改善進行詳細的觀察測量；第三，我們不但使用電腦化的 CANTAB 作為完整評估患者執行功能障礙的工具，而且我們也使用健康受試者在 CANTAB 的表現作為常模，將患者的測驗分數轉換成 z-score，以客觀比較患者

用藥前後的執行功能表現是否有顯著差異。

4.2.3. 結論

總結來說，我們的研究發現 ADHD 患者在經過 12 週的 atomoxetine 治療後，除了行為症狀有明顯的改善之外，其執行功能與視覺記憶障礙也有顯著的進步，包括注意力、抑制能力、注意力轉換能力、空間短期記憶、工作記憶、空間計畫與解決問題能力、形態辨認記憶、以及空間辨認記憶等，然而即使在 12 週追蹤期間結束時，ADHD 患者上述的執行功能與視覺記憶表現並未回復至正常水平，因此長期使用 atomoxetine 對於提升 ADHD 患者的執行功能和視覺記憶是有效果的，而這些認知功能的改善將有助於 ADHD 患者更有效地進行課業學習，並增加其人際社會功能。

4.3 注意力不足過動症的執行功能障礙與神經影像學

4.3.1. 討論

使用DSI的方法，我們發現ADHD患者兩側額葉紋狀體神經路徑之完整性均有缺損的現象，因為與對照組相比較，ADHD患者額葉紋狀體神經路徑的擴散係數GFA較低，可能有許多病理因素會造成這個現象，例如神經纖維排列組織不規則、神經軸突的變性退化 (degeneration)、或者神經髓鞘化 (myelination) 缺損等 (Beaulieu, 2002; Mori & Zhang, 2006)，而我們的研究結果與過去DTI的結果一致 (Ashtari et al., 2005; Liston et al., 2011; Pavuluri et al., 2009)，表示額葉紋狀體神經路徑完整性的缺損可作為ADHD的生物標記。

過去的腦部影像研究發現 ADHD 患者左側前額葉的灰質 (Shaw et al., 2009) 和白質 (Mostofsky et al., 2002) 有缺損，而我們的研究進一步發現 ADHD 患者額葉紋狀體神經路徑的左側化現象有障礙，在健康受試者之額葉紋狀體神經網路的左側化現象可能與正常的認知功能有關，包括了選擇性注意力以及避免被外界不

相干刺激所吸引 (Weissman & Banich, 1999)，因此我們的研究結果顯示除了整體的額葉紋狀體神經路徑缺損之外，額葉紋狀體神經路徑的左側化不足也可能在 ADHD 的病理生理機轉方面扮演重要角色 (Rubia et al., 2000)。

我們的研究發現右側 orbitofrontal 神經路徑的完整性和注意力不足症狀之間具有顯著相關，這項結果與 ADHD 的注意力控制缺損的認知模式相符合 (Castellanos et al., 2006)，最近的研究顯示若增加右側 orbitofrontal 皮質與其它腦區的功能性聯結，則會提升受試者注意力的調控 (Diekhof et al., 2009)，另外也有研究發現右側 orbitofrontal (McCrea, 2009) 與 caudate (L. E. Campbell et al., 2009) 的異常會導致顯著的注意力障礙，綜合上述的研究結果，我們推論 ADHD 患者右側 orbitofrontal 神經路徑的缺損可能導致了臨床上的注意力不足症狀。

除了 ADHD 患者的注意力不足症狀之外，我們也發現左側 dorsolateral 與右側 medial prefrontal 神經路徑的完整性與過動衝動症狀具有顯著相關性，這項結果與過去的腦部影像學研究結果相符合，因為在左側 DLPFC 的體積下降被發現與過動衝動症狀有關連性 (Kates et al., 2002; Mostofsky et al., 2002; L. J. Seidman, 2006)，而 Spalletta 等人則發現左側 DLPFC 的腦部血液灌流量下降，會與過動症狀有相關 (Spalletta et al., 2001)，這些證據都顯示左側的 dorsolateral 神經路徑在臨床上的過動衝動症狀扮演著重要角色。

根據我們的了解，這是世界上第一篇研究探索 ADHD 患者額葉紋狀體神經路徑缺損與執行功能障礙之間的關係，整體而言，我們的結果發現 ADHD 患者在進行 CANTAB 測驗時所呈現的執行功能障礙，與額葉紋狀體神經路徑缺損之間具有顯著的相關。就個別的測驗來看，由 ADHD 患者在 IED 測驗所顯示的注意力轉換障礙，與左側 orbitofrontal 和 ventrolateral 神經路徑完整性有明顯相關，因此我們的研究結果支持額葉紋狀體神經迴路對於認知的靈活性 (flexibility) 是十分重要的 (Kehagia et al., 2010)。早期的研究發現巴金森氏症患者在進行 IED 測驗時會有明顯的障礙，這代表額葉與基底核的異常可能會導致注意力轉換能力的下降 (Downes et al., 1989)，而 Owen 等人則發現接受額葉切除手術的病人，其

注意力轉換能力會有明顯障礙 (Owen et al., 1991)，此外，最近的腦部影像學研究發現注意力轉換能力與特定腦區的活性有相關，包含 VLPFC (Hampshire & Owen, 2006; Shafritz et al., 2005)、anterior cingulate cortex (Shafritz et al., 2005)、紋狀體 (Shafritz et al., 2005)、以及額葉紋狀體迴路 (Monchi et al., 2001) 等，此外，OFC 也曾被報告與注意力轉換能力的調節有關 (Kehagia et al., 2010)，綜合來說，orbitofrontal 與 ventrolateral 神經路徑的異常有可能參與了 ADHD 患者的注意力轉換障礙的病理生理機轉。

若要在 RVP 測驗上有適當的表現，需要受試者有好的持續注意力、抑制控制能力、以及自我監測能力，Coull 等人使用正子斷層造影 (Positron Emission Tomography，PET) 技術，發現當受試者在進行 RVP 測驗時，腦部會有幾個特定區域的活化，包括下額葉腦迴 (inferior frontal gyrus)、頂葉、梭狀腦迴 (fusiform gyrus)、以及輔助性運動區域 (supplementary motor area) 等 (Coull et al., 1996)，功能性的腦部造影研究則顯示與 RVP 測驗表現關係最顯著的區域是額葉頂葉區 (fronto-parietal regions) (Lawrence et al., 2003)，而我們的研究發現左側 orbitofrontal 神經路徑的完整性與 RVP 測驗的表現具有顯著相關性，綜合來說，OFC (Elliott & Deakin, 2005; Rubia et al., 2010)、基底核 (Jahfari et al., 2011; H. S. Liu et al., 2011)、以及其間的神經路徑，在 ADHD 患者的持續注意力和抑制能力障礙方面扮演著重要角色。

早期的研究發現那些接受額葉切除手術的患者在 SWM 的測驗表現會有明顯障礙 (Owen et al., 1990)，此外，多發性硬化症 (multiple sclerosis) 患者在 SWM 測驗的表現與其額葉病灶的大小呈現顯著相關 (Foong et al., 1997)，而我們的研究則發現 ADHD 患者在 SWM 測驗的表現與左側 orbitofrontal 神經路徑的完整性有相關，這項結果與過去許多的研究結果一致，例如 Wolf 等人曾報告成人 ADHD 患者在進行工作記憶測驗時，其 orbitofrontal 部位的活化會有不足的現象 (Wolf et al., 2009)，du Boisgueheneuc 等人則發現空間工作記憶障礙和位於左側額葉的病灶有關 (du Boisgueheneuc et al., 2006)，而我們的研究也延伸了 Vestergaard 等人

的發現，左側額葉頂葉網路 (frontoparietal network) 的擴散係數 FA 和 SWM 測驗的表現有關 (Vestergaard et al., 2011)。

早期的研究報告顯示，腦部額葉受損的患者在進行 SOC 的測驗時會出現空間計畫能力的障礙 (Shallice, 1982)，Owen 等人也發現那些接受額葉切除手術的患者在進行 SOC 測驗時，會出現思考時間遲滯的現象 (Owen et al., 1990)，Rowe 等人的研究也發現當受試者進行空間計畫測驗時，其思考時間與左側額葉的局部血液灌流量呈現明顯的相關性 (Rowe et al., 2001)，後來的功能性腦部造影研究也證實了前額葉與基底核在空間計畫能力上扮演著重要的角色 (Beauchamp et al., 2003; S. D. Newman et al., 2009; Rowe et al., 2001)，我們的研究則更進一步顯示 ADHD 患者空間計畫與問題解決能力和左側 orbitofrontal 以及 dorsolateral 神經路徑的完整性有顯著相關性，過去使用 Tower of London 來評估受試者空間計畫能力的研究發現，在進行測驗時腦部 orbitofrontal 區域有明顯活化的現象 (Elliott et al., 1997; Rowe et al., 2001)；至於 dorsolateral 區域，Curtis 等人則發現 DLPFC 會參與將注意力導向計畫思考與問題解決的流程 (Curtis & D'Esposito, 2003)，若是 DLPFC 出現明顯病灶，則會導致組織與規劃能力的障礙 (Makris et al., 2007)，綜合來說，ADHD 患者空間計畫與問題解決能力和左側 orbitofrontal 以及 dorsolateral 神經路徑的完整性確實有顯著的相關性。

至於神經傳導物質方面，我們的研究顯示注意力不足症狀與大多數的執行功能障礙都和 orbitofrontal 神經路徑的完整性有明顯相關，過去的研究發現 orbitofrontal 區域有許多來自 mesolimbic 與 mesocortical 多巴胺神經系統的分布 (Depue & Collins, 1999)，多巴胺神經傳導系統的異常已被發現和 ADHD 患者的注意力不足症狀 (Genro et al., 2010; Shang & Gau, 2011) 與執行功能障礙 (A. F. Arnsten & B. M. Li, 2005) 有關，我們的研究結果也間接支持了異常的多巴胺系統可能是透過影響額葉紋狀體的神經迴路，進而造成了 ADHD 患者的臨床症狀與執行功能障礙。

4.3.2. 研究限制及優點

我們的執行功能障礙與神經影像學研究有以下幾項研究限制，第一，由於我們的研究是橫斷性設計 (cross-sectional study design)，所以無法確切判定我們在 ADHD 患者所觀察到的額葉紋狀體神經路徑異常，究竟是 ADHD 的病因，或者是因為 ADHD 所導致的代償性結果 (compensatory consequences)，因此需要後續長期追蹤研究來探索額葉紋狀體神經路徑異常與 ADHD 之間的因果關係；第二，我們的研究只分析額葉紋狀體的完整性，但可能還有其它神經路徑的異常與 ADHD 有關，例如額葉-顳葉網路 (frontotemporal networks) (A. Konrad et al., 2010)、或額葉-紋狀體-頂葉-小腦網路 (fronto-striato-parieto-cerebellar networks) (Rubia et al., 2009)，因此需要後續研究來探討其它的神經路徑和 ADHD 之間的關係；第三，我們的研究中有 18 個 ADHD 患者正在使用藥物治療，雖然這些患者在接受核磁共振掃描前須至少停藥一週，但我們仍然無法完全排除長期使用 ADHD 治療藥物對於腦部額葉紋狀體神經路徑的影響，因此未來需要針對未曾服用 ADHD 治療藥物的 (drug naive) 患者加以研究，以避免藥物對腦部可能產生的長期影響；第四，由於我們使用患者組與對照組年齡配對的研究設計，因此我們無法檢驗年齡對於額葉紋狀體完整性的影響，未來應針對不同年齡之 ADHD 患者加以研究比較，以探討發展年齡在 ADHD 患者額葉紋狀體完整性所扮演的角色。

4.3.3. 結論

總結來說，我們的研究發現 ADHD 患者左右兩側額葉紋狀體神經路徑 (也就是 dorsolateral-caudate、medial prefrontal-caudate、orbitofrontal-caudate 和 ventrolateral-caudate) 的完整性有明顯缺損，並且這些缺損和 ADHD 的臨床症狀以及執行功能障礙有顯著相關性，未來影像基因學的研究將有助於進一步探索額葉紋狀體迴路、執行功能、和 ADHD 致病基因彼此之間的關係。

4.4 注意力不足過動症的基因遺傳學

4.4.1. *DAT1* 基因與注意力不足過動症的相關性研究

4.4.1.1. 討論

我們的研究在 DAT1 基因上所發現的三個單套體區間與國外的研究有相同但也有相異的地方 (Brookes et al., 2006; Friedel et al., 2007; Genro et al., 2008)，例如我們與過去的研究均發現最後一個單套體區間是以為 3′UTR 終點，雖然 DAT1 位於靠近第五條染色體的端粒 (telemere)，這通常會提高基因重組 (recombination) 的可能性，但 Greenwood 等人也發現，DAT1 基因在不同族群仍然保有相當高的一致性 (Greenwood et al., 2002)，這可以解釋為何我們的研究與國外的研究有相似的發現。但另外一方面，這些研究彼此之間也有一些差異，例如我們發現在第二個單套體區間包含了位於第八個內顯子 (rs27048) 與第十一個內顯子 (rs429699) 的 SNP，但 Friedel 等人則並未報告 rs27048 被包含於任何的單套體區間之內 (Friedel et al., 2007)，而 Genro 等人則發現第三個單套體區間包含了位於第十四個內顯子的 SNP (rs40184) (Genro et al., 2008)，但我們的研究則並未發現這個 SNP 位於任何一個單套體區間之內，這些研究結果的差異反應了不同 SNP 彼此之間連鎖不平衡的複雜關係 (Greenwood et al., 2002)，因此在檢驗 DAT1 基因時應找出適當的 SNP，以便能探索 DAT1 基因與 ADHD 之間的相關性。

我們的研究發現 DAT1 基因的 SNP (rs429699) 與單套體 (rs27048 (C) /rs429699 (T)) 和 ADHD 注意力不足亞型之間具有顯著的相關性，在量性分析方面也顯示單套體 (rs27048 (C) /rs429699 (T)) 和注意力不足症狀的嚴重程度有關，而過去的研究也發現 DAT1 基因與 ADHD 注意力不足亞型 (Krause et al., 2003) 和注意力症狀 (K. Konrad et al., 2010) 有相關性，除了 DAT1 基因之外，也有其它的基因被報告與 ADHD 注意力不足亞型有關，包括 5HT1B (Smoller et

al., 2006) 和 alpha-2a-adrenergic receptor (Schmitz et al., 2006) 基因等。雖然 Waldman 等人曾發現 DAT1 基因和 ADHD 的過動衝動症狀較有關聯 (Waldman et al., 1998)，但我們的研究並未發現 DAT1 基因上的任何 SNP 或單套體與過動衝動症狀有關。另外我們的研究並未發現 DAT1 與 ADHD 的混合亞型有關聯，這點和 Wohl 等人的研究一致 (Wohl et al., 2008)，但與其它團隊的研究結果則不相同 (Asherson et al., 2007; Genro et al., 2008)，這些差異性可能是由於以下幾方面因素所造成，包括基因標記的挑選、樣本的大小、以及 ADHD 本身的臨床異質性等。

雖然我們發現 DAT1 基因上的變異與 ADHD 有顯著的相關性，但我們並沒有直接對這些變異進行功能性分析，因此這些變異與 ADHD 之間是否有因果關係仍有待驗證。雖然內顯子的基因變異不會影響氨基酸的序列，但近來有愈來愈多的研究顯示內顯子的變異在 DAT1 的基因表現上扮演著重要的角色 (Greenwood & Kelsoe, 2003; Kouzmenko et al., 1997)，例如 Kouzmenko 等人發現第一個內顯子的序列會參與 DAT1 基因在神經細胞內的表現 (Kouzmenko et al., 1997)，而 Greenwood 等人則發現 DAT1 基因上的第九、第十二、以及第十四個內顯子的變異可以導致 DAT1 基因表現量增為兩倍 (Greenwood & Kelsoe, 2003)。

在各種不同的族群研究顯示，3´UTR 的 10-repeat allele 在華人、蒙古人、以及日本人的比例較歐洲人的比例為高 (Mitchell et al., 2000)，而我們的樣本顯示 10-repeat allele 的比例為 91.6%，與過去在華人族群所作的研究相一致 (Chen et al., 2003; Cheuk et al., 2006; Qian et al., 2004)，因此代表我們的研究並無抽樣偏差的存在 (selection bias)。而基於我們的研究與過去其它的研究 (Gizer et al., 2009; D. Li et al., 2006; Purper-Ouakil et al., 2005)，只有很薄弱的證據顯示 3´VNTR 的 10-repeat allele 與 ADHD 之間有相關性，雖然有兩個 meta-analysis 發現 3´VNTR 與 ADHD 之間並無相關性 (D. Li et al., 2006; Purper-Ouakil et al., 2005)，但 Gizer 等人的研究則發現 10-repeat allele 和 ADHD 之間有些微的相關性 (勝算比為 1.12)

(Gizer et al., 2009)，因此 3´VNTR 的基因變異可能不是直接導致 ADHD 的病因，而是代表一個靠近真正病因的標記 (Greenwood & Kelsoe, 2003)，或者 3´VNTR 是透過與環境的交互作用而造成 ADHD (Brookes et al., 2006)。

4.4.1.2. 研究限制及優點

我們的基因遺傳學研究有以下幾項研究限制，第一，我們的樣本若再區分為不同的 ADHD 亞型，特別是過動衝動亞型，則檢定力會相對變小，因此未來仍需要針對不同的亞型收集更多的樣本；第二，我們的研究只有探索一個特定的 DAT1 基因，對於像 ADHD 這樣的複雜疾病，應該不是只由單一基因所造成的，因此未來仍需要針對不同的基因加以研究；第三，我們的 ADHD 樣本是來自門診轉介，因此研究結果是否能類推至一般的族群，這需要進一步的研究設計加以驗證。

4.4.1.3. 結論

總結來說，我們的研究發現 DAT1 基因上的一個單套體區間與 ADHD 的注意力不足亞型有相關性，支持了多巴胺系統在 ADHD 的病理生理學方面扮演重要角色。我們的研究結果顯示在進行 ADHD 分子遺傳學研究時應先收集同質性高的樣本，這樣將可以比較容易發現致病的基因變異。

4.4.2 *DAT1* 基因與執行功能障礙之相關性

4.4.2.1. 討論

雖然動物研究 (Pioli et al., 2008) 和人類研究 (Mehta et al., 2001) 都顯示了多巴胺在調節空間工作記憶上扮演重要角色，但是只有很少的研究特別探討 DAT1 與空間工作記憶之間的關係，由於 DAT 是 ADHD 的主要治療藥物 methylphenidate 的作用部位，而過去已有報告顯示 methylphenidate 可以提升健康

受試者 (Elliott et al., 1997) 與 ADHD 患者 (Kempton et al., 1999; Mehta et al., 2004; Turner et al., 2005) 的空間工作記憶測驗的表現，而我們的研究證實了 DAT1 基因與空間工作記憶之間確實具有相關性。空間工作記憶和腦部的特定區域有關，包括前額葉 (Nelson et al., 2000; van Asselen et al., 2006)、後頂葉 (Klingberg et al., 2002; Koch et al., 2005)、以及海馬迴 (Abrahams et al., 1999) 等，雖然 DAT1 基因主要是表現在紋狀體，而在前額葉、後頂葉、以及海馬迴的表現量較少 (Diamond, 2007; Durston et al., 2005; Schott et al., 2006)，但仍有幾方面的證據顯示 DAT1 基因會透過紋狀體和皮質的神經分布來影響空間工作記憶，第一，當進行工作記憶測驗時，紋狀體的多巴胺功能和前額葉的活性呈現明顯的相關性 (Landau et al., 2009)；第二，腦部影像學已證實工作記憶測驗的表現牽涉的不只是前額葉，而是整個額葉、紋狀體、以及頂葉等區域 (Stollstorff et al., 2010)；第三，功能性腦部造影顯示，DAT1 的基因變異與進行工作記憶測驗時的神經活性有明顯的相關性 (Bertolino et al., 2006; Bertolino et al., 2009; Stollstorff et al., 2010)，綜合上述研究結果，我們可以推論說在進行工作記憶測驗時，前額葉與頂葉的活性仍然會受到 DAT1 基因變異的影響。

我們的研究發現半套體 rs403636 (G) /rs463379 (C) /rs393795 (C) /rs37020 (G) 與 SWM 的 within-search errors 8 boxes 和 double errors 8 boxes 有顯著相關，根據我們過去的執行功能研究，我們發現當測驗難度增加時，ADHD 患者的執行功能障礙會變得更加明顯 (Gau et al., 2009)，神經影像學研究也顯示當工作記憶測驗的難度增加時，前額葉與紋狀體參與的程度也會增加 (C. Chang et al., 2007; Wager & Smith, 2003)，Stollstorff 等人也發現，當工作記憶測驗的難度增加時，腦部的活性會因為 DAT1 基因型的不同而有不同的反應。未來需要針對半套體 rs403636 (G)/ rs463379 (C)/ rs393795 (C)/ rs37020 (G)與 ADHD 患者的多巴胺活性之間的關係，進行更深入的功能性研究。

除了工作記憶之外，我們的研究並未發現 DAT1 基因與其它的執行功能有相關性，包括空間廣度、注意力轉換作業、以及空間計畫等。雖然已經有許多研究

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指出多巴胺在注意力轉換能力方面扮演重要角色 (Robbins & Arnsten, 2009)，並且注意力轉換能力與 DBH (Barkley et al., 2006) 和 COMT (Schulz et al., 2011) 等基因都有相關，然而過去的研究並未發現 DAT1 基因與注意力轉換能力之間具有相關性 (Barkley et al., 2006; Boonstra et al., 2008; Karama et al., 2008; Schulz et al., 2011)，因此相對於前額葉的多巴胺系統，Schulz 等人推論紋狀體的多巴胺系統對於注意力轉換能力的影響較小 (Schulz et al., 2011)。

4.4.2.2. 研究限制及優點

我們的執行功能障礙與 DAT1 基因研究有以下幾項研究限制，第一，我們只有探索一個基因與空間工作記憶的關係，而過去在不同的精神疾病研究發現，空間工作記憶與 DRD3 (Ersche et al., 2011)、COMT (Nagel et al., 2008)、Dysbindin (Donohoe et al., 2007)、MAOA (Rommelse et al., 2008)等基因都有相關，未來分析其它基因將有助於我們對於 ADHD 患者空間工作記憶障礙的病因有更全面的了解；第二，我們研究中所使用的神經心理測驗主要是測量 ADHD 患者的執行功能障礙，未來應探討 DAT1 基因對於其它神經心理功能障礙的影響。

4.4.2.3. 結論

總結來說，我們的研究發現 DAT1 基因與 ADHD 患者的空間工作記憶有相關性，由於 methylphenidate 可以改善 ADHD 患者的空間工作記憶障礙，因此未來需要進一步檢驗我們所發現的半套體變異與 methylphenidate 藥物反應之間的關係，另外由於空間工作記憶是 ADHD 患者的內表現型，因此未來可以透過功能性腦部造影來探索 DAT1 基因對於神經迴路的影響。

5. 展望 (Prospect)

5.1 藥物基因學

　　雖然臨床研究已經顯示藥物治療對於 ADHD 的成效，但仍然有許多患者的療效並不明顯，並且在藥物的耐受性與接受度方面存有許多差異。若了解 ADHD 治療效果的相關基因預測因子，將會有助於未來的臨床治療，包括對不同的患者給予最適當的藥物治療、以及事先找出可能會產生藥物治療副作用的患者。近年來由於研究工具的不斷進步，已經有愈來愈多的研究探討藥物與基因之間的關係，因而形成藥物基因學 (pharmacogenetics) 的研究 (Kieling et al., 2010)，藉此更深入探討 ADHD 的病理生理機轉。過去的研究焦點集中在藥物反應與 DAT1 基因型之間的關係，因為 DAT1 基因所轉譯合成的蛋白質 dopamine transporter 正是治療 ADHD 的藥物 methylphenidate 作用的位置，但這些研究卻顯示了不一致的結果，例如有些研究發現，DAT 基因在 3´UTR 的位置若有 10-repeat allele，則個案會有較佳的藥物反應 (Stein et al., 2005)。但也有研究顯示相反的結果，即 10-repeat allele 反而與較差的藥物反應有相關性 (Winsberg & Comings, 1999)，而其它研究則顯示 10-repeat allele 與藥物反應之間並無相關性 (Langley et al., 2005)，過去的結果之所以會有這樣的差異，可能與研究設計上的不同有關，另外像藥物劑量的使用方式以及結果測量 (outcome measure) 的工具，都有可能產生這些研究結果的差異。

　　除了 DAT1 之外，另外一個常在研究 ADHD 藥物基因學的目標是 DRD4 基因，最早的報告是 Winsberg 等人發現 ADHD 患者的 DRD4 之 7-repeat allele 基因型與 methylphenidate 的療效之間並無明顯的相關性 (Winsberg & Comings, 1999)，而 Seeger 等人則發現若是 ADHD 患者同時帶有 DRD4 上的 7-repeat allele 以及 serotonin transporter 基因的 long allele，則對於 methylphenidate 的療效反應較差 (Seeger et al., 2001)。除了 7-repeat allele 之外，4-repeat allele 是 DRD4 上常

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被探討的基因變異，Cheon 等人發現兒童 ADHD 患者若是帶有 4/4 的基因型，則在接受 8 週的 methylphenidate 之後，患者會有比較好的藥物反應 (Cheon et al., 2007)，未來仍需要針對 DRD4 上的不同基因型探討與藥物反應之間的關係。

過去大多數的 ADHD 藥物基因學研究都是探討 methylphenidate 的療效，只有很少數的研究是分析基因與 atomoxetine 療效之間的關係 (Ramoz et al., 2009; Trzepacz et al., 2008)。Trzepacz 等人分析 CYP2D6 基因的 poor metabolizer 與 extensive metabolizer 之間的療效與藥物劑量，結果發現 poor metabolizer 使用 atomoxetine 的劑量比 extensive metabolizer 要低 0.1mg/kg，但在臨床治療上往往不需要事先知道 ADHD 患者的 CYP2D6 的基因型，臨床醫師也能根據症狀改善的情形來適當地調整 atomoxetine 的劑量 (Trzepacz et al., 2008)。由於 atomoxetine 是作用在 norepinephrine transporter 上，因此 NET 基因是 atomoxetine 的藥物基因學的重要目標，Ramoz 等人發現在經過 6 週的 atomoxetine 治療之後，ADHD 患者的 NET 基因上若是帶有某些 SNPs，則其療效會顯著提高 (Ramoz et al., 2009)，未來需要針對 NET 基因進行詳細的基因變異鑑定，以期發現更具顯著性的藥物反應標記。

未來 ADHD 的藥物基因學研究除了可以針對上述這些因素加以控制之外，也需要對不同的基因、不同的藥物 (如 atomoxetine)、以及基因與基因的交互作用等議題加以探討，將更能了解基因型與 ADHD 的藥物反應之間的關係，而這些研究結果將有助於個人化醫療 (individualized medicine) 的發展，未來可根據 ADHD 個案不同的基因型來選擇最合適的藥物治療，以提升治療效果並降低副作用的發生。

雖然目前對於 ADHD 藥物基因學的研究正在增加，但針對過去的研究結果呈現出彼此不一致的現象，我們認為這可能反應了 ADHD 患者在基因型與表現型上的異質性，此外過去採取二分法的測量方式以及回溯性的研究設計，可能都會導致無法偵測到有意義的基因型差異。因此設計前瞻性的研究，同時採取量化的測量方式，都是應當進行的研究方向。因此我們的藥物基因學研究收集 160

位 7-18 歲未曾使用過藥物治療的 ADHD 患者，這些患者將被隨機分配至兩個治療組，其中 80 人接受 methylphenidate，另外 80 人接受 atomoxetine，在一年的治療期間內將會規則地評估藥物的療效，主要的療效評估工具為 SNAP-IV (父母版與老師版)，其他評估療效的量化工具則包含 Achenbach Youth Self-report (YSR)、Child Behavior Checklist (CBCL)、Clinical Global Impressions-ADHD-Severity (CGI-ADHD-S)、Clinical Global Impressions-ADHD-Improvement (CGI-ADHD-I)、Social Adjustment Inventory for Children and Adolescents (SAICA)、以及 Chinese version of the Family Adaptation, Partnership, Growth, Affection, and Resolve (Family APGAR-C)等。另外根據過去我們的 ADHD 內表現型研究結果，患者也將接受神經心理測驗，包含魏氏兒童智力測驗、持續注意力測驗、以及 CANTAB 等，同時我們將收集所有受試者的 DNA 樣本，並針對可能會影響藥物效果的相關基因 (DAT1, DRD4, DRD5, NET, COMT) 進行鑑定。所有患者將接受長達 24 週的定期追蹤，希望能詳細評估藥物短期和長期的療效，並探索影響藥效的相關基因變異。

　　在高淑芬教授的指導之下，我們的藥物基因學研究在 2009 年獲得國科會三年個人型計畫的補助 (NSC 98-2314-B-002-051-MY 3)，並於 2009 年至 2012 年順利完成 160 位 ADHD 患者的收案，目前所有患者已完成 24 週的追蹤。我們預期本研究將在台灣本土的樣本上建立 ADHD 的藥物基因學，並找出藥物治療效果與基因變異之間的關聯性。藉著不同的測量方式所找出不同基因型對藥物反應的作用，將會幫助我們更加了解 ADHD 的病理生理機轉，未來根據患者個別的基因型所發展的個人化治療將會有效減輕病症、改善耐受性、以及增加藥物遵從度。相反地，若是患者帶有與療效不佳或顯著副作用相關的基因型，則可以避免接受沒有益處的藥物。我們的藥物基因學研究在發展新的 ADHD 治療藥物方面也具有重要的潛力，使用基因篩檢來決定藥物劑量的方式可以提供未來藥物發展的新模式，因為將可以根據不同的基因型，而非只是不同的藥物，來評估療效之間的差異性。

5.2 結構性與功能性神經影像學

整合過去的神經影像學研究結果，ADHD 患者最常被報告異常的腦部區域為前額葉、dACC、striatum 及小腦。dorsolateral 及 ventrolaterl prefrontal cortex 均和許多執行功能相關，像是注意力、計畫、工作記憶等能力，而 ventrolateral prefrontal cortex 又和行為抑制相關；dACC 屬於報償迴路 (reward circuit) 的一部分，其功能和注意力、行為抑制、覺察錯誤及動機相關；striatum 被認為和執行功能及報償迴路均有相關；小腦開始被發現和認知功能相關，其功能仍有待釐清。而 ADHD 患者最常被報告異常的神經纖維束為額葉紋狀體迴路，但單一迴路並不能解釋 ADHD 患者的高異質性，包括 superior longitudinal fasciculus (Ashtari et al., 2005; Hamilton et al., 2008; A. Konrad et al., 2010; Makris et al., 2008; Pavuluri et al., 2009)、以及 inferior longitudinal fasciculus (A. Konrad et al., 2012; Pavuluri et al., 2009) 等神經路徑完整性的障礙，也曾被過去的 DTI 研究發現與 ADHD 的症狀有相關性，因此仍有待更多研究去了解除了額葉紋狀體以外其他的神經纖維束在 ADHD 患者的障礙。在高淑芬教授的指導之下，我們的研究團隊已經收集了 40 位兒童 ADHD 患者以及 40 位健康對照組，並且每個受試者都接受詳細的臨床症狀評估、神經心理功能測驗、以及 DSI 的核磁共振造影，未來我們將比較 ADHD 患者和健康對照組之間，在 superior longitudinal fasciculus 以及 inferior longitudinal fasciculus 神經路徑的完整性上是否有差別，希望能找到除了額葉紋狀體之外其它與 ADHD 有關的神經路徑異常。

雖然我們過去在 DSI 的研究已發現額葉紋狀體的神經路徑完整性與 ADHD 的症狀和執行功能障礙之間有相關性，但 DSI 是屬於結構性神經影像造影，若要更全面地了解 ADHD 的中樞神經障礙，除了結構性神經影像造影之外，應該也要同時針對 ADHD 患者的腦部神經網路進行功能性神經影像造影研究。在功能性神經影像造影研究中，PET 是其中一項重要的研究工具，PET 的原理是利用

不同的放射性物質，可以提供腦部的葡萄糖代謝及腦部灌流的資訊，也可用於研究 dopamine 的代謝及 dopamine 相關的受器（dopamine transporter 以及 dopamine D$_2$ receptor），但因為 PET 研究有放射線的問題，在倫理上不適合用於兒童及青少年的研究，近年來分析腦部灌流時，已逐漸用核磁共振技術取代 PET。

目前功能性神經影像學研究中，fMRI 是最常被用來作為研究的工具，因為 fMRI 可以呈現腦部血氧濃度的狀態，可間接反應出神經活動的狀態，提供在不做任何測驗時的預設模式網絡 (default-mode network) 的造影 （又稱為 resting-state fMRI），以及呈現做認知測驗時的腦部活動區域。同時活動的腦區即是在功能上相聯結的區域，而功能相聯結的腦區之間，推測應該有神經纖維束的聯結，即神經結構上的聯結 (van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009)。預設模式網絡是指在休息的狀態下仍有持續的腦部活動，這個網絡包含了 precuneus / posterior cingulate cortex、前額葉中央部位及頂葉 (parietal lobe) 等區域，而預設模式網絡在做測驗時活性會下降，若活性無法正常地下降，認知測驗則容易出錯。而不同的認知測驗，會引發不同腦區的活動，這些共同活動的腦區即是功能上相關的區域。之前的研究發現不論是在預設模式網絡或是做認知測驗時，ADHD 患者的腦部活動在神經結構異常的部分 （前額葉、頂葉、紋狀體、小腦） 也發現和正常人有差異，但活性較高或較低的結果都有被報告，其中常被提出的異常為 fronto-striatal 及 fronto-cerebellar 功能性聯結 (K. Konrad & Eickhoff, 2010)。

在 2007 年時，Sonuga-Barke 與 Castellanos 等人曾經提出 ADHD 是一種預設模式網絡疾病 (default network disorder) (Sonuga-Barke & Castellanos, 2007)，因為 ADHD 的預設模式網絡無法被其它的神經網路系統加以調節，因此會對正在進行的神經心理活動造成干擾，進而表現為 ADHD 患者的認知功能障礙 (Castellanos et al., 2005)，Fassbender 等人也證實 ADHD 患者腦部的預設模式網絡無法被適當地抑制 (Fassbender et al., 2009)。Peterson 等人則更進一步研究發現，對於 16 位 ADHD 患者給予 methylphenidate 治療後，其腦部在前額葉和 posterior

cingulate cortex 的預設模式網絡可以回復正常的被抑制現象 (Peterson et al.,

2009)，而 Liddle 等人發現 ADHD 患者腦部預設模式網絡的正常抑制現象，會明

顯受到 methylphenidate、動機的高低 (報酬的高低)、以及診斷之間交互作用的影

響 (Liddle et al., 2011)，也就是說當接受 go/no-go 測驗時，對照組的孩子不論在

高或低報酬的情境下，都能有效地降低預設模式網絡的活性，但是對於沒有服用

methylphenidate 的 ADHD 患者來說，只有在高報酬的情境下才能有效地降低預

設模式網絡的活性，若是服用 methylphenidate 之後，ADHD 患者不論在高或低

報酬情境下均能有效降低預設模式網絡的活性 (Liddle et al., 2011)，整體來說，

這些研究結果顯示在 ADHD 患者腦部的預設模式網絡、認知控制網路、以及邊

緣系統網路 (limbic network) 之間，有著彼此複雜互動的關係，並且會影響到整

體的神經迴路功能，而不是只有單一網路系統異常的問題，因此未來若同時進行

結構性與功能性神經影像學的探索，將能更加全面地了解 ADHD 腦部的神經聯

結與神經網路障礙。

　　紐約大學的兒童研究中心 (Child Study Center) 是目前國際上公認為 ADHD

神經影像學的權威機構，其團隊領導人 Castellanos 教授在近二十年發表了數十

篇關於 ADHD 腦部功能性神經影像學的研究，大大提升了兒童精神醫學界對於

ADHD 神經網路障礙的了解，其論文均刊登在 Impact Factor 極高的國際期刊中，

因此學生計畫在 2013 年到 2014 年間至 Castellanos 教授的團隊學習先進的功能

性神經影像學，在未來這一年的研修時期，學生希望除了能學習如何分析 resting

state functional MRI 的資料之外，還能整合構造性的神經聯結與功能性神經聯結

之間的關係，進而學習如何整合各個不同的研究領域，包括神經影像學、神經心

理學、基因遺傳學、以及臨床診療等等，進而形成一個更加全面的 ADHD 的神

經生物學理論。

5.3 影像基因學

根據我們過去的研究發現，ADHD 患者有基因變異與腦部神經路徑完整性的異常，因此未來我們計畫藉由影像基因學 (imaging genetics) 的研究，來深入探索基因型變異對腦部結構障礙所產生的影響，並了解 ADHD 由基因變異到神經系統異常的生理病理機轉。過去研究發現在 ADHD 個案以及其未發病的手足，若其 DAT1 基因在 3´UTR 的位置有 10-repeat allele，則腦部影像顯示紋狀體 (striatum) 的 dopamine transporter 活性較低 (Durston et al., 2008)。也有功能性腦部影像研究發現，當操作神經心理測驗時，DAT1 基因在 3´UTR 的位置上帶有 10-repeat allele 的 ADHD 患者，其大腦背測前扣帶皮質 (dorsal anterior cingulate cortex) 活性較低 (Brown et al., 2010)。Waldman 等人也發現，若是神經系統原本處於多巴胺活性過低的狀況下，DAT1 基因的過度表現將會導致 ADHD 症狀的嚴重度增加 (Waldman et al., 1998)。上述這些研究均顯示，ADHD 腦部功能的異常與基因型之間具有非常密切的關聯性，同時這些研究結果也發現，多巴胺的活性太高或太低都有可能產生腦部神經調節作用的異常，進而導致注意力不足或過動衝動的症狀 (Durston, 2010)。

除了 DAT1 基因之外，另外最常被研究的是針對 DRD4 基因與 ADHD 神經影像的關係進行探討。早期的研究使用體積作為腦部變化的測量目標，但並未發現 DRD4 的基因型對於 ADHD 患者的腦部體積有顯著的影響 (Bobb et al., 2005; Castellanos et al., 1998)。但最近的研究則是針對 DRD4 在腦中特別會表現的部位進行影像基因學的研究，例如 Shaw 等人發現在 DRD4 基因第三個外顯子 (exon III) 上若是帶有 7-repeat allele 的個案，右側前額葉以及後頂葉的腦部皮質較薄 (Sheridan et al., 2007)。另外有研究指出，帶有此 7-repeat allele 的 ADHD 個案，其小腦皮質也顯著較薄 (Monuteaux et al., 2008)，這些研究結果都證實了 DRD4 基因確實會對 ADHD 腦部特定區域產生明顯的影響。

除了DAT1與DRD4這兩個基因之外，過去也有少數的影像基因學研究探討其它的catecholamine基因對於ADHD患者神經障礙的影響 (Baehne et al., 2009; Bobb et al., 2005)。Bobb等人曾針對12個候選基因與ADHD的關係進行研究，結果發現

DRD1與NET這兩個基因和ADHD之間具有顯著的相關性 (Bobb et al., 2005)，更進一步他們探索這些基因變異是否會影響ADHD患者腦部特定區域的體積，結果發現腦部的體積與這些候選基因之間並無明顯的相關性 (Bobb et al., 2005)。Baehne等人則是研究tryptophan hydroxylase gene (TPH2) 的基因變異 (Baehne et al., 2009)，TPH2參與了神經傳導物質serotonin的合成，而serotonin在ADHD的病理機轉中也扮演重要角色，而Baehne等人發現TPH2的基因型確實和前額葉的腦波異常有顯著相關性 (Baehne et al., 2009)。

由於影像基因學是一門新的研究領域，到目前為止只有很少數專門針對ADHD 的影像基因學相關研究，主要的焦點也都是集中在前面所提到的 DAT1 與 DRD4 這兩個候選基因對腦部所產生的影響，而且研究結果缺乏一致性 (Durston, 2010)。由於基因的變異會直接影響基因的表現，而現代影像學研究的發展讓我們可以直接在腦部造影中看見在不同腦區這些基因的表現情形，這也是基因影像學的一大優勢，但這些研究也有其內在的限制，因為基因影像學的取向太過簡化腦部在發展過程所顯示的複雜性，由基因變異到腦部結構或功能的異常，中間往往會受到許多其它發展因子的影響，而 ADHD 是發展性疾病 (developmental disorder)，因此應該考慮基因與外在環境在腦部成長過程中的交互作用，才能真正了解基因對神經網路異常所產生的影響。未來需要更多的影像基因學研究來針對不同的基因並控制相關因素，以發現這些基因型造成 ADHD 患者在腦部結構與功能方面的異常的機制。

在高淑芬教授的指導之下，我們的研究團隊已經收集了 40 位的兒童 ADHD 患者，經過隨機分配為兩組，一組服用 methylphenidate，另一組則服用 atomoxetine，在用藥之前先進行 MRI 造影，在用藥 12 週之後再進行一次 MRI 造影，同時我們也有收集受試者的血液並進行 DNA 的純化，接下來我們將進行後續的分析，同時探討基因、神經迴路、以及藥物作用三者之間的關係，以更全面了解 ADHD 的病理生理機轉。

5.4 動物模式

　　動物模式的定義是必須出現與要研究的疾病相同的行為表現型 (Sontag et al., 2010)，由於 ADHD 的診斷必須在行為表現型上出現注意力不足、過動、以及衝動等核心症狀，因此 ADHD 的動物模式 (animal model) 也應該要反應這三方面的症狀。整體而言，過去的動物研究顯示 ADHD 的症狀與單胺 (monoaminergic) 神經傳導系統的異常有關，其中經常被研究的是多巴胺和正腎上腺素系統異常的動物模式 (Russell, 2007)，而最具代表性的 ADHD 動物模式則是 SHR (spontaneously hypertensive rats)。根據神經傳導物質的研究顯示，SHR 的腦部正腎上腺素系統 (noradrenergic systems) 有很明顯的改變 (Russell, 2001)，這可能與某些基因表現的異常有關 (Reja et al., 2002)，而且 SHR 之前額葉的多巴胺濃度會下降，因此在腦部正腎上腺素與多巴胺濃度的不平衡下，SHR 會表現 ADHD 的核心症狀。除了外在的表現型之外，神經心理學測驗也顯示 SHR 有認知功能的缺損。例如與對照組相比，當延遲給予增強物時，SHR 較不容易產生新的學習反應 (Hand et al., 2006)，並且 SHR 在空間記憶 (spatial memory) 的能力表現較弱，在聽覺刺激測驗中，SHR 顯示較少的驚嚇反應 (startle response)，上述這些神經認知功能的異常，有助於進一步了解 ADHD 的神經生理學變化。

　　雖然 SHR 在許多方面都顯示是一個非常有價值的 ADHD 動物模式，但過去也有研究指出，在其它方面的表現 SHR 並不能完全代表 ADHD，例如在某些專注力測驗中 (five-choice serial reaction time test)，SHR 並未呈現較差的反應，而且在藥物反應的研究中，SHR 並未顯示對 methylphenidate 的行為測驗改善效果 (van den Bergh et al., 2006)，因此以 SHR 為動物模式研究 ADHD 時，也應當注意人類腦部生理病理變化的複雜性，並不能用單一的動物模式解釋。

　　另外 DAT1 knockout 的老鼠缺乏 DAT1 基因，也常被用來作為 ADHD 的動物模式 (Sontag et al., 2010)，這些 DAT1 knockout 的老鼠會出現行為過動 (Gainetdinov & Caron, 2001; Gainetdinov et al., 1999; Giros et al., 1996) 的症狀以

及空間記憶功能 (Gainetdinov & Caron, 2001; Gainetdinov et al., 1999) 上的缺損，而這些症狀主要是與多巴胺的清除率下降有關 (Jones et al., 1998)，雖然 DAT1 knockout 的老鼠有上述類似 ADHD 的症狀，但目前並沒有證據支持 ADHD 患者的 dopamine transporter 有下降的現象，反而有許多研究顯示在 ADHD 患者之紋狀體的 dopamine transporter 反而是上升的現象 (Cheon et al., 2003; Krause et al., 2000)，因此這也是 DAT1 knockout 老鼠作為 ADHD 的動物模式的缺點。

除了老鼠以外，其它的動物模式也曾用於 ADHD 的研究中，例如暴露於多巴胺的神經毒素 (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP) 的猴子，除了會出現注意力不足症狀，同時在神經心理學測驗方面顯示有注意力轉移作業 (shifting attentional sets) 以及時間知覺 (time perception) 的障礙 (Decamp & Schneider, 2004)，因此經過 MPTP 處理的猴子也被認為適合作為 ADHD 注意力不足亞型的動物模式。未來我們的研究團隊將根據 ADHD 患者的基因研究結果，發展有效的動物模式，以深入探討 ADHD 在神經傳導物質與神經結構方面的生物學異常。

6. 論文英文簡述 (English summary)

The doctoral thesis summarizes that the research results of the author in the neurobiological and genetic studies on ADHD. The main strategies include neuropsychological, pharmacological, neuroimaging, and genetic association approaches.

6.1 Neuropsychological dysfunction in ADHD

6.1.1 Neuropsychological dysfunction

Introduction

Attention-deficit/hyperactivity disorder (ADHD), a common early-onset neuropsychiatric disorder (Gau et al., 2005), is recognized to have multiple cognitive dysfunctions (Willcutt et al., 2005), particularly in executive functions. Among them, the most consistent results are tasks requiring abilities of planning (e.g., Tower of Hanoi) and inhibition (e.g., Stroop test), followed by tasks requiring subjects to shift efficiently (e.g., Wisconsin Card Sorting Test), then tasks concerning fluency (e.g., letter and design fluency) with negative findings (Pennington & Ozonoff, 1996). Recent literature has documented that executive functions has discriminative validity for ADHD with moderate effect sizes (Willcutt et al., 2005), and with greater reductions in the visuo-spatial executive functions than the verbal working memory (Martinussen et al., 2005).

The prefrontal cortex develops dramatically in adolescence, and this development has significant influence on the cognitive control (Blakemore &

Choudhury, 2006). Although executive function deficits appear to continue across the life span from childhood into adolescence, there is still relatively little information in adolescents with ADHD, which has yielded mixed results as to the degree and domains of executive dysfunctions (Barkley et al., 2001). For example, Barkley and the colleagues found that adolescents with ADHD showed no deficits in working memory or response inhibition, which questioned whether executive dysfunctions were as robust in adolescents as in children with ADHD (Barkley et al., 2001). It warrants to investigate of adolescents with ADHD to clarify whether executive function deficits reflect a delay in maturation or a persistent weakness (Martel, et al., 2007). As the majority of previous studies are conducted in Western populations, their results may not be generalized to other ethnic groups, such as the Chinese population. The current study aimed to investigate the verbal and non-verbal executive functions of adolescents with childhood diagnosis of ADHD and to examine the effect of the level of task difficulties, persistent ADHD, psychiatric comorbidity, and use and treatment duration of methylphenidate on executive functions in adolescents.

Materials and Methods

The sample included 53 11-16 year-old adolescents (40 males and 13 females, mean age at follow-up=12.7±1.4), who were observed to have overt ADHD symptoms at mean age of 4.8±1.7 years old, were clinically diagnosed with DSM-IV ADHD at mean age of 7.6±2.9 at the Children's Mental Health Center, Department of Psychiatry, National Taiwan University Hospital (NTUH), Taipei. Fifty-three comparison adolescents (controls) were recruited from the same school district and were matched for sex, age, intelligence, and parental educational levels of the ADHD group.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) tests

were administered by a psychologist (Chiu CD), who had be trained to administer the CANTAB following the standard protocols at a laboratory designed for the CANTAB assessment at NTUH. The testing lasted approximately 90 minutes, and was administrated at a fixed schedule to all participants. Four tasks of the CANTAB involving executive abilities were employed in this study, including Spatial Span (SSP), Spatial Working Memory (SWM), Intra-Extra Dimensional Shift (IED), and Stockings of Cambridge (SOC).

The descriptive results were displayed as frequency and percentage for categorical variables; for continuous variables, mean and SD. To conduct a matched case-control analysis for the binary variables, we used conditional logistic regression to compare the rate of psychiatric disorders at adolescence between the case and control groups, and to calculate the odds ratio (OR) and 95% confidence interval (CI) by employing the Proc Glimmix procedure of the SAS 9.1 (SAS Institute Inc., Cary, NC, USA). For the continuous variables, we used the linear multi-level model to compare the mean scores of the performance of each CANTAB test and IQ. For those tests with different levels of difficulties (SWM and SOC), we further adjusted the repeated measures within the same subjects while we examined the interaction between group and the task difficulty levels. Alpha value was pre-selected at the level of $p < 0.05$. The effect sizes (standardized difference between two means) were further computed using Cohen's *d*. We defined small, medium, and large effect sizes as Cohen's *d* 0.3 to 0.5, 0.5 to 0.8, and > 0.8, respectively. In addition to the comparisons between the two groups, we also test the effect of persistent ADHD, comorbidity, current use and duration of methylphenidate treatment on the executive function in the ADHD group.

Results

The ADHD group had significantly more total usage errors than the controls. There was no difference in total errors and spatial span length. The ADHD group needed more trials to complete the stages than the controls. There were no group differences in the maximum number of stages completed, pre-ED shift errors, and ED shift errors. The ADHD group had significantly more total number of errors in searching the box with blue token than the controls, particularly in 6- and 8-box problems with small to medium effect sizes. There was no group difference in strategy utilization. The ADHD group had significantly fewer problems solved in the minimum number of moves. Three additional measures were compared by the two groups, and tested for the interaction between group and within task difficulty levels (i.e., 2-, 3-, 4-, and 5-move problems). Our results showed that the ADHD group had more total moves, particularly in 5-move problem; shorter total initial thinking time; and shorter total subsequent thinking time, particularly in 5-move problem than the controls.

Discussion

As the first to examine neuropsychological functioning in a Han Chinese adolescent population, this study lends evidence to support the non-verbal executive dysfunctions measured by the CANTAB (such as short-term spatial memory, spatial working memory, set-shifting, spatial planning, and problem-solving) in adolescents with childhood diagnosis of ADHD, particularly in the executive tasks with increased demands, regardless of IQ score, use of methylphenidate, persistent ADHD and psychiatric comorbidity (Martinussen et al., 2005).

Previous ADHD studies have criticized the construct of executive functions as weakly defined and overly broad (Pennington & Ozonoff, 1996). Although the present study did not employ all but several domains of executive functions, our findings

demonstrated similar effect sizes (*d*=0.4~0.6) of executive dysfunctions in the ADHD group to those found in the majority of previous studies (Willcutt et al., 2005). Our findings did not support the dysfunctional behavioral inhibition as a single deficit in ADHD proposed by Barkley (Barkley, 1997) but deficits in several key domains of executive functions (Willcutt et al., 2005). Our hypothesis of deficits in non-verbal executive function in ADHD as revealed by Western studies (Pennington & Ozonoff, 1996) have gained support from the findings of deficits in spatial short-term memory, working memory, set-shifting, and problem solving measured by the CANTAB (Kempton et al., 1999).

Major methodological limitations of this study are relatively small sample size, only recruitment of clinical participants with ADHD, and neuropsychological assessments at follow-up only. Although our sample size is larger than earlier studies, it is not sufficient to fully explore the heterogeneity of ADHD. A clinic-based sample limits the generalization of our results. However, a meta-analysis has shown that the mean effect sizes (*Cohen's d* = 0.49 ± 0.06) on the executive function measures in the community studies are only slightly smaller than those (*Cohen's d* = 0.56 ± 0.04) in the clinic studies (Willcutt et al., 2005), suggesting that the relation between executive dysfunction and ADHD was not restricted to clinic-referred samples.

Implications

Despite reductions in ADHD symptoms, deficits in executive function, which has negative impact on academic performance, remained at adolescence. Assessment of executive dysfunction at adolescence in children with ADHD is recommended to provide important information that cannot be extracted from assessments of psychopathology; therefore, early identification and prevention for the adverse outcome of ADHD and executive deficits at adolescence can be achieved. We strongly

recommend extra assistance and educational intervention to these children while the complex tasks are assigned to them. Future studies will be carried out to examine the neuropsychological functioning other than executive functioning in a larger sample to explore the heterogeneity of ADHD.

6.1.2 Neuropsychological endophenotypes

Introduction

Despite substantial evidence supporting the genetic etiology of ADHD (Faraone, 2000), molecular genetic studies, even using ADHD subgroup approaches such as comorbidity, persistency, and subtype, so far have not provided any conclusive results. To address these challenges, there has been growing interest in using endophenotypes such as neuropsychological, neuroimaging, and electrophysiological paradigms (Doyle et al., 2005) for ADHD genetic studies. Among them, neuropsychological functioning is recognized as a valuable endophenotype for ADHD genetic studies.

Some studies have shown decreased performance in some domains of neuropsychological functions in unaffected siblings or other relatives of patients with ADHD (Rommelse, Van der Stigchel et al., 2008; L. J. Seidman et al., 2000); deficits in attentional control (D. I. Slaats-Willemse et al., 2007) and response inhibition (D. Slaats-Willemse et al., 2003) were found in unaffected relatives of ADHD, evidencing the familial overlap of ADHD and executive dysfunction. However, executive functions have not been comprehensively assessed among unaffected siblings of patients with ADHD and no study has examined the neuropsychological functions in unaffected siblings of ADHD patients using the CANTAB.

In addition to executive fucntion, several rationales endorse further examination of deficits in visual memory as ADHD endophenotypes. First, there is growing

evidence for poor performance on visual memory tasks in ADHD, including

impairment in spatial recognition memory (Kempton et al., 1999), delayed matching

to sample (Barnett et al., 2009), pattern recognition memory (S. M. Rhodes et al.,

2004), and paired associates learning (H. T. Chang et al., 1999). These studies support

the extension of the range of neuropsychological deficits associated with ADHD to

visual memory functioning. Second, for neuropsychological measures to be useful

endophenotypes for ADHD, they should demonstrate evidence of heritability.

Although data on the heritability of specific neuropsychological functions are limited,

the heritability of visual memory is estimated as 0.53, somewhat greater than those for

verbal and perceptual speed abilities (Alarcon et al., 1998). Third, despite no

improvement in performance on executive tasks (S. M. Rhodes et al., 2006),

methylphenidate is effective in improving visual memory performance in children

with ADHD (S. M. Rhodes et al., 2004, 2006). Fourth, no data on visual memory

function have been reported in unaffected siblings.

In summary, the literature on neurocognitive impairments in unaffected relatives

is inconsistent with small effect sizes. The CANTAB, which has not previously been

used in studies of ADHD relatives, may have greater power than clinically

administered measures to detect the subtle deficits we expect to see in unaffected

siblings because it is a computerized battery that captures the reaction time of

responses as well as errors in a wide range of executive functions. An investigation of

the executive function and visual memory as potential endophenotypes for ADHD in

a large, ethnic Han Chinese population in Taiwan by comprehensively assessing the

verbal working memory, non-verbal executive functions, and visual memory using the

CANTAB in ADHD adolescents, their behaviorally unaffected siblings, and

unaffected controls, is warranted. We hypothesized that unaffected siblings, similar to

adolescents with ADHD, are more likely to have deficits in executive functions and

visual memory than unaffected healthy controls.

Materials and Methods

The sample consisted of 279 probands with ADHD, 108 unaffected siblings, and 173 school controls. The probands were 279 patients (male, 85.7%) who had had overt symptoms noted at ages 4.2±1.6 years and were clinically diagnosed with DSM-IV ADHD at the mean age of 6.7±2.9 years. They were recruited consecutively mainly from the child psychiatric clinic of National Taiwan University Hospital (*n*=240, 86%). Their current and lifetime ADHD and other psychiatric diagnoses were confirmed by the *Chinese Kiddie epidemiologic version of the Schedule for Affective Disorders and Schizophrenia (K-SADS-E)* interview at the mean age of 12.5±1.6 years. We recruited 108 unaffected biological siblings, who were 8 years old or older and assessed by using the *Chinese K-SADS-E* at the mean age of 12.2±3.3 years; and 173 controls (male, 72.8%) from the same school district as the ADHD probands, who were assessed to be without lifetime ADHD by inquiring into childhood and current symptoms using the *Chinese K-SADS-E* at the mean age of 12.6±1.5 years. All participants who had a clinical diagnosis of psychosis or autism spectrum disorders or an intelligence quotient (IQ) score less than 80 were excluded.

Four tasks of the CANTAB involving executive abilities were employed in this study, including SSP, SWM, IED, and SOC. Inaddition, four visual memory tasks were employed, including Delayed Matching to Sample (DMS), Spatial Recognition Memory (SRM), Pattern Recognition Memory (PRM), and Paired Associates Learning (PAL).

The three comparison groups were probands with ADHD, unaffected siblings, and school controls. The descriptive results were displayed as frequency and percentage for categorical variables, and for continuous variables, mean and SD. We

used a multi-level model with random and fixed effects to address the lack to independence of the probands and their siblings within the same family. The Proc Glimmix procedure with binomial distribution and logit link for the non-linear mixed model was used to compare the rate of psychiatric disorders. We used a linear multi-level model to compare the CANTAB performance and the Bonferroni method to adjust p values in post hoc analysis due to multiple comparisons, and we controlled for sex, age, IQ, comorbidity, and parental educational levels in the statistical model. For those tests with different levels of difficulty (SWM and SOC), we adjusted the repeated measures within the same subjects while we examined the interaction between the group and task difficulty. We used the Goodness of Fit test to compare the model treating the three groups in an order ranging from unaffected controls, unaffected siblings to ADHD probands, and as a categorical variable to the model treating the three groups as an ordinal variable. We found that the three groups can be treated as an ordinal variable. Then we tested the significance of the linear trend across the three groups in an order ranging from unaffected controls, unaffected siblings to ADHD probands on the CANTAB performance.

Results

ADHD probands had significantly fewer digits recalled forward (*Cohen's d*, 0.25) and backward (*Cohen's d*, 0.48) than unaffected controls. Unaffected siblings recalled fewer digits backward than unaffected controls. ADHD probands (as well as unaffected siblings) had more EDS errors, and more total raw and adjusted errors than unaffected controls, with small effect sizes. The significant differences, except total raw errors, disappeared in multivariate analyses. Both univariate and multivariate analyses revealed that ADHD probands (*Cohen's d*, 0.67) and unaffected siblings (*Cohen's d*, 0.46) had significantly shorter span sequences successfully recalled than

unaffected controls; and ADHD probands had more total usage errors than the other two groups, with small effect sizes. ADHD probands and unaffected siblings showed poorer use of strategy, with small effect sizes, and had more total errors in searching the box than the controls, with medium effect sizes; the significant differences were the same in the 4-, 6- and 8-box searches. The majority of patterns of significant differences remained in multivariate analyses, except for the 4-box search. ADHD probands and unaffected siblings solved fewer problems in the minimum number of moves, mean moves, and shorter initial thinking time, with small to medium effect sizes (absolute Cohen's d, 0.33 ~ 0.56), particularly in the 4-move and 5-move tasks. The majority of patterns of significant differences remained in multivariate analyses.

In DMS, ADHD probands and their unaffected siblings had higher probability of an error following a correct response and following an error response than the controls. Unaffected siblings had fewer number of correct responses in total (d, -0.46) and all delays (d, -0.46) than the controls. In SRM, both univariate and multivariate analyses revealed that ADHD probands had fewer percent of correct responses than the controls (d, -0.49) without group difference in mean latency of correct response. There were no significant differences in SRM performances between unaffected siblings and probands with ADHD, or between unaffected siblings and controls. In PAL, ADHD probands had more adjusted total errors, more total trials to success, and lower first trial memory scores (absolute values of Cohen's d, 0.41–0.48). All the patterns of significant differences disappeared in multivariate analyses. There were no significant differences in PAL performances between unaffected siblings and probands with ADHD, or between unaffected siblings and controls. In PRM, we did not find significant group differences in percentage of correct responses. But ADHD probands had shorter mean latency of correct responses than the controls in multiple analyses.

Discussion

The current study is the first to comprehensively examine executive functions, which consisted of low (spatial span and digit span forward) and high (verbal and spatial working memory) executive tasks, by using the CANTAB and digit spans in a large sample of ADHD probands and their unaffected siblings. Our findings consistently demonstrated that despite no obvious ADHD symptoms, unaffected siblings, like ADHD probands, performed significantly worse than unaffected controls in verbal working memory measured by digit spans backward, and in the majority of non-verbal executive functions, such as spatial short-term memory, spatial working memory, spatial planning, and response inhibition, measured by the CANTAB. These findings indicate the significant familiarity of executive dysfunction in ADHD, consistent with the idea that subtle cognitive traits may be more closely linked to the underlying genetic factors than the behavioral phenotype (D. I. Slaats-Willemse et al., 2007). And, this strongly implies that executive functions measured by the digit span backward and the CANTAB fulfill some of the important criteria of an endophenotype (Doyle et al., 2005): executive dysfunctions co-occur with ADHD and are manifested in unaffected relatives. The CANTAB is also shown to be a suitable instrument with good psychometric properties. Our results suggest that studies on executive dysfunction in ADHD probands and their unaffected siblings can shed light on the effort to explore the genetic etiology of this disorder (Nigg et al., 2004).

Although individual measures of executive function, such as response inhibition (D. Slaats-Willemse et al., 2003), have been identified as potential endophenotypes for ADHD, the use of isolated measures may be problematic and the results may be inconsistent across settings. In contrast, our findings have shown that a range of

executive function components may be relevant to the familial risk for this disorder. Because children with ADHD show a range of deficits on measures of executive function, a comprehensive battery approach is assumed to be maximally informative.

In addition, our results provide strong evidence to support that visual memory measured by the DMS can be cognitive endophenotype for ADHD. Our findings demonstrated that in univariate analyses, unaffected siblings, like ADHD probands, performed significantly worse than controls in visual memory measured by the DMS task. In multivariate analyses, unaffected siblings occupied an intermediate position between the ADHD probands and the controls in probability of an error following a correct response and following an error response in the DMS, and in percent of correct responses in the SRM. Although the impairments in visual memory were modest in unaffected siblings and the tasks in the CANTAB are multifactorial (Robbins et al., 1994), to the best of our knowledge, this is the first study documenting that visual memory measured by the CANTAB may be a useful cognitive endophenotype for ADHD.

The major methodological limitation is the questionable generalization of our findings to community-based samples. Moreover, as a naturalistic design, although the currently medicated participants held medication for at least 24 hours before receiving neuropsychological tests, the concerns about the medication effect on the executive function remain. However, given that many ADHD children receive pharmacotherapy, the executive function of treated samples is relevant to clinical practice (L. J. Seidman et al., 1997). Moreover, the use of only one verbal task (digit span forward and backward) is another limitation of this study. Lastly, this study is limited by the fact that the majority of patients (86%) were male. Hence, further studies of relatives of females with ADHD are warranted.

Implication

Our findings imply that several measures of executive function and visual memory function may constitute novel cognitive endophenotypes for ADHD. Our findings also support the sensitivity and usefulness of the CANTAB tasks in assessing the executive function and visual memory deficits in ADHD probands and their unaffected siblings. In addition, the executive function and visual memory as endophenotype approach may increase the power to detect susceptibility loci and candidate genes, and can also be used as a paradigm for functional brain imaging studies in ADHD.

6.2 Neuropsychological endophenotypes and atomoxetine in ADHD

Introduction

Atomoxetine, a highly selective noradrenaline reuptake inhibitor (SNRI), is a potent inhibitor of the presynaptic norepinephrine transporter, with little affinity for other noradrenergic receptors or for other neurotransmitter transporters (Simpson & Perry, 2003). Atomoxetine augments prefrontal norepinephrine levels without increased catecholamine levels in nucleus accumbens (Bymaster et al., 2002), which may underlie the addictive properties of stimulants (Koob & Le Moal, 1997), the first approved medications by the Food and Drug Administration (FDA) in the United States for treating ADHD. Atomoxetine was approved by the FDA as the first nonstimulant substance for treating ADHD in the United States in 2002. Previous studies have shown its efficacy in reducing clinical symptoms of ADHD (Gau et al., 2007).

Human studies have demonstrated that a single clinically relevant oral dose of atomoxetine was associated with decreased stop-signal reaction time in healthy

participants (Samuel R. Chamberlain et al., 2006) and adults with ADHD (S. R. Chamberlain et al., 2007), and decreased commission errors in adults with ADHD (S. R. Chamberlain, Muller et al., 2007). Despite the growing clinical use of atomoxetine in children, only one pilot study reported significant effect of atomoxetine on sustained attention measured by the Rapid Visual Information Processing task in nine children and young people with ADHD (Barton et al., 2005).

Animal studies have shown that norepinephrine efflux is selectively increased during a task measuring spatial memory (Rossetti & Carboni, 2005), suggesting that norepinephrine may be involved in the active maintenance of visuo-spatial information. Activation of neuronal circuits related to norepinephrine release contributed to a significant enhancement of performance on visual memory in rats (Clayton & Williams, 2000). Moor et al. have found that intravenous infusion of norepinephrine improved visual recognition memory in healthy participants (Moor et al., 2005). Animal studies showed that atomoxetine decreased the errors in visual recognition memory (radial arm maze) (Tzavara et al., 2006) and the number of perseverative errors (visual discrimination test) (Seu et al., 2009).

Hence, we conducted the current study to assess the long-term efficacy of atomoxetine on the improvements of executive functioning measured by five CANTAB tasks, and visual memory measured by two CANTAB tasks as the primary aim and on the symptom reductions as the secondary aim in 30 boys with ADHD. We hypothesized that atomoxetine would improve performance on the CANTAB tasks with prominent executive and visual memory demands in addition to ADHD-related symptom reductions.

Materials and Methods

We recruited 30 drug-naive male patients aged 8-16 (mean ± standard deviation,

SD, 10.70 ± 1.84) with clinically diagnosed DSM-IV ADHD from the Children's Mental Health Center of National Taiwan University Hospital, Taipei, consecutively. The participants and their mothers were interviewed by using the *Chinese version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Epidemiological Version (K-SADS-E)* to confirm the participants' DSM-IV diagnoses of ADHD and other psychiatric disorders.

Five CANTAB tasks involving executive abilities were employed in this study, including SSP, IED, SWM, RVIP, and SOC. Two visual memory tasks were employed, including PRM and SRM.

Using a sample of 180 normally developing children, aged 8-16, without DSM-IV diagnosis of ADHD based on the Chinese K-SADS-E as the norm for the CANTAB assessments, we transformed the raw score of each parameter to its z-score, which has a mean of zero and a SD of 1, by using the mean and SD derived from the norm. The data of the CANTAB were expressed by mean ± SD of the raw scores and z-scores; the data of the CGI-ADHD-S and self-administered measures (SNAP-IV and CPRS-R:S) were expressed by mean ± SD of the raw scores and *t*-scores, respectively. The *t*-score was defined by multiplying the *z*-score by 10 and adding 50 with a mean of 50 and a SD of 10 (*t*-score = *z*-score x 10 + 50). Because the repeated measures within the same subject, we used a linear multi-level model to test the mean differences in the repeated measures of the executive functions measured by the CANTAB tasks,the CPRS-R:S, the SNAP-IV and the CGI-ADHD-S at Week 4 and Week 12, as compared to baseline (Week 0), and to test the interactions between visits and the task difficulties.

Results

At baseline, the mean CGI-ADHD-S rating was "markedly ill" to "severely ill"

(5.57 ± 0.73). The score significantly decreased to 3.43 ("mildly ill" to "moderately ill") at Week 4, and to 2.83 ("borderline ill" to "mildly ill") at Week 12 (Table 3), with a significant linear trend of decreasing symptom severity. Regarding parental ratings, children with ADHD had significant score reductions in the Chinese CPRS-R: S and SNAP-IV-Parent forms from baseline to Week 4 (Cohen *d*, -0.51~-0.90) and Week 12 (Cohen *d*, -0.80~-1.15) except in the oppositional subscales, which showed significantly reductions at Week 12 with small effect sizes.

In IED, the pre-EDS errors, EDS errors, and adjusted total trials and errors significantly decreased at Week 4 from baseline with medium effect sizes. The EDS errors and adjusted total errors and trials were significantly lower and more stages were completed at Week 12 than at baseline with small to medium effect sizes. In RVIP, children with ADHD had more total hits, fewer total misses, higher probability of hits, total correct rejections, better sensitivity to errors, and shorter mean latency to respond correctly at Week 4 and Week 12 than at baseline (Cohen *d* ranging from 0.35 to -0.80). There were more total correct rejections [Cohen *d*, 0.21; mean z-score difference (95% CI), 0.33 (0.04, 0.61)] and shorter mean latency to respond correctly [Cohen *d*, -0.39; mean z-score difference (95% CI), -0.51 (-0.79, -0.23)] at Week 12 than at Week 4. In SSP, children with ADHD had longer span sequences successfully recalled at Week 12, and fewer total usage errors at Week 4 and Week 12 than at baseline with medium effect sizes. In SWM, children with ADHD utilized fewer strategies to improve searching efficacy and had fewer total errors at Week 12 than at baseline with small effect size. There was marginally significant interaction between the three visits and the task difficulties (4-, 6-, and 8-box problems) on the total errors (regression coefficient estimate, $\beta = -1.25$, $p = .062$). In SOC, the participants had fewer moves, more problems solved in the minimum number of moves, and shorter initial and subsequent thinking time at Week 12 than at baseline (Cohen *d* ranging

from -0.35 to -1.12). Moreover, they had more problems solved in the minimum number of moves at Week 12 than at Week 4 [Cohen d, 0.57; mean z-score difference (95% CI), 0.58 (0.26, 0.90)]. Their initial and subsequent thinking time was shorter at Week 4 as compared to baseline. There were marginally significant interaction between the three visits and the task difficulties (2-, 3-, 4-, and 5-move problems) on the mean moves ($\beta = -0.10$, $p = .053$) and the subsequent thinking time ($\beta = 2.19$, $p = .044$).

For the PRM task, the mean latency of correct responses decreased (Cohen's d, -0.50) and total correct responses increased (Cohen's d, 0.53) significantly at Week 4 from baseline. The mean latency of correct responses also significantly decreased at Week 12 from baseline (Cohen's d, -0.50). The mean latency of correct responses of the SRM task significantly decreased at Week 12 from baseline (Cohen's d, -0.42), but there was no significant change in correct responses.

Discussion

The current study is the first to examine the efficacy of atomoxetine in children with ADHD (Barton et al., 2005) using a wide-range of executive tasks of the CANTAB with a greater sample size, longer follow-up, and more visits than previous human studies (Barton et al., 2005; S. V. Faraone et al., 2005). The major finding was that atomoxetine was effective in improving a variety of non-verbal executive functions in boys with ADHD including sustained attention (RVIP), inhibitory ability (RVIP), attentional set shifting (IED), spatial short-term memory (SSP), spatial working memory (SWM), and spatial planning (SOC), mainly noted at Week 4 and lasting to Week 12 except that significant improvement in performance of SSP. SWM, and probably SOC was noted at Week 12. Moreover, the magnitude of improvement in spatial planning and problem solving was a function of treatment duration of

atomoxetine and task difficulties. Hence, our results lend strong evidence to support the findings from animal studies (L. A. Newman et al., 2008) and previous human studies (S. V. Faraone et al., 2005) that atomoxetine is an effective treatment for the executive dysfunction associated with ADHD, not only in Western populations (S. V. Faraone et al., 2005), but also in an ethnic Han Chinese population, and not only in adults (S. R. Chamberlain et al., 2007) but also in children. Consistent with previous clinical trials (Gau et al., 2007), our findings also demonstrate the efficacy of atomoxetine in reducing ADHD-related symptoms based on two well-validated parental rating scales and investigator's assessments.

Unlike the negative findings in adults with ADHD (T. Spencer et al., 1998), the present study demonstrated the association of atomoxetine with some visual memory functions measured by the PRM and SRM tasks. This disparity may be related to differences in the mean age of participants and the paradigms deployed. The sample in this present study (8–16 years old) was much younger than that reported by Spencer et al. (19–60 years old). We used two CANTAB visual memory tasks whereas Spencer et al. used one (Rey-Osterrieth Complex Figure).

The neuropsychological profile suggests that atomoxetine may be functionally distinct from conventional psychostimulants, with different effects on the visual memory. The significant association of atomoxetine with the mean latency for correct responses on the PRM task found in the current study was not seen with methylphenidate (S. M. Rhodes et al., 2004). Our findings support the evidence from an animal study that at doses relevant to those that increased cortical norepinephrine release, atomoxetine improved pattern recognition in rats (Tzavara et al., 2006). Additionally, in contrast to no improvements on the SRM task with stimulant treatment (Kempton et al., 1999), our findings showed that atomoxetine was associated with enhanced performance on this task in terms of speeding up correct

responses. Our finding further supports norepinephrine playing an important role in regulating the spatial recognition memory (Zhang et al., 2008). Taken together, improvement in the latency for correct responses on the PRM and SRM tasks with atomoxetine suggests a more important role for norepinephrine than for dopamine in the cognitive processes required for optimal performance on these visual memory tasks.

Several methodological limitations should be considered when interpreting the findings. The sample size and male subjects only have limited our ability to examine the differential efficacy of atomoxetine on executive function and visual memory as a function of sex, ADHD subtypes or comorbid patterns. Next, as a repeated measure design, the vulnerability of tests to factors as loss of novelty and learning effects has been highlighted (Lowe & Rabbitt, 1998). The high stability (high ICC no mean difference for one-month test-retest reliability) of the CANTAB suggests that evidence of strong change in the CANTAB performance could safely be interpreted as due to atomoxetine treatment effects rather than to random inter-temporal fluctuations neuropsychological functioning. Furthermore, longer follow-up period up to 12 weeks compared to previous studies minimized the practice effect. Last, although this study demonstrated the effectiveness of atomoxetine in improving executive functioning and visual memory, head-to-head comparison of atomoxetine with psychostimulants warrants further investigation and functional brain imaging studies are needed to explore the precise effects of atomoxetine on the neural circuitry of executive function and visual memory.

Implication

Our findings indicate that in addition to symptoms reductions, atomoxetine is also efficacious in improving a variety of non-verbal executive functions and visual

memory. However, their performance at the endpoint is still not normalized. Therefore, long-term administration of atomoxetine is recommended for improving executive functions and visual memory, which may mediate the amelioration of the academic performance and social functioning in children with ADHD, particularly when they face difficult and complicated tasks and situations.

6.3 Neuroimaging in ADHD

Introduction

The evidence that ADHD is associated with neurobiological deficits in the frontostriatal network (T. J. Spencer et al., 2002) has been demonstrated from morphometric studies showing reduced prefrontal, caudate nucleus, putamen, and globus pallidus (Overmeyer et al., 2001) volume and cortical thickness (Shaw et al., 2006); and functional imaging studies showing frontal and striatal hypoperfusion and hypoactivity (Dickstein et al., 2006). Recently, diffusion tensor imaging (DTI) has been used to investigate the microstructure integrity of white matter tracts (Ashtari et al., 2005; A. Konrad et al., 2010). Fractional anisotropy (FA) is usually used as an index to reflect white matter integrity (Johansen-Berg & Behrens, 2009). Abnormal white matter microstructures relevant to ADHD have been found by DTI in various regions including the frontostriatal tract (Ashtari et al., 2005; A. Konrad et al., 2010), cerebellum (Ashtari et al., 2005), superior longitudinal fasciculus (A. Konrad et al., 2010) and the corticospinal tract (Hamilton et al., 2008). Among those regions, disturbed frontostriatal microstructural integrity is recognized as the most consistent finding in ADHD.

Despite considerable interest in both ADHD and DTI research, to our best knowledge, there has been no study to correlate the microstructural integrity of

frontostriatal tracts and a wide range of executive functions or to use diffusion

spectrum imaging (DSI) to reconstruct frontostriatal tracts and to probe

microstructural abnormalities along these tracts that may be related to the functional

deficits observed in children with ADHD. In contrast to DTI, DSI is able to resolve

crossing fibers by performing more comprehensive diffusion measurements than DTI

(Wedeen et al., 2005). Tractography reconstructed from DSI data has been

successfully demonstrated to resolve crossing fiber tracts (Wedeen et al., 2008).

Using a matched case-control study design, the present study aimed to compare

the executive functions and microstructural integrity and asymmetry patterns of the

four frontostriatal tracts, i.e., dorsolateral-caudate, medial prefrontal-caudate,

orbitofrontal-caudate, and ventrolateral-caudate tracts, comparing the DSI

tractography of children with ADHD and typically developing children, and to

investigate whether the white matter tract integrity of frontostriatal circuit was

directly correlated with ADHD symptoms and executive functions. We hypothesized

that frontostriatal connectivity was involved in ADHD pathophysiology and that

disturbed frontostriatal fiber integrity was correlated with ADHD symptoms and

executive functions.

Materials and Methods

We recruited 25 Taiwanese children with ADHD consecutively from the child

psychiatric clinic of National Taiwan University Hospital, Taipei, Taiwan, and 25

typically developing children matched individually for age, sex, handedness, and

full-scale IQ from the schools with similar school districts to the ADHD group rather

than through advertisement. All participants were right-handed, as assessed with the

Edinburgh Inventory (Oldfield, 1971). Children with ADHD were clinically

diagnosed according to the DSM-IV criteria and confirmed by the *Chinese Kiddie*

epidemiologic version of the Schedule for Affective Disorders and Schizophrenia (K-SADS-E) interview. Four CANTAB tasks involving executive abilities were used to assess the non-verbal executive function, including IED, RVP, SWM, and SOC.

Participants were scanned on 3T MRI system (Trio, Siemens, Erlangen, Germany) with a 32-channel head coil. DSI was performed using a twice-refocused balanced echo diffusion echo planar imaging sequence (Reese *et al.,* 2003), TR/TE = 9100 ms/142 ms, image matrix size = 128×128, spatial resolution = 2.5 mm × 2.5 mm, slice thickness = 2.5 mm. A total of 102 diffusion-encoding gradients with the maximum diffusion sensitivity bmax = 4000 s mm^{-2} were sampled on the grid points in a half sphere of the 3D $\mathbf{q}$-space with $|\mathbf{q}| \leq 3.6$ units. To divide the frontostriatal fiber tracts into four tract bundles corresponding to different cortical regions in bilateral hemispheres, five regions of interest (ROI) were identified using MARINA software (Bender Institute of Neuroimaging, University of Giessen, Germany). These five regions were the caudate nucleus, DLPFC, MPFC, OFC, and VLPFC on the Montreal Neurological Institute (MNI) template. Linear transformation between non-attenuated image (b_0) of DSI and T2W image, and non-linear transformation between T2W image and MNI template were performed so that the image coordinates of DSI data could be transformed to the MNI space. The coordinates of the ROIs defined on the MNI template were then mapped onto individual participants' DSI data through the inverse transformation using the calculated deformation matrix. The tractography was reconstructed by using in-house software (DSI Studio: http://dsi-studio.labsolver.org). Tract-specific sampling of GFA was performed using an in-house mean-path analysis algorithm developed in Matlab (The Mathworks, Natick, MA, USA).

The descriptive results were displayed as frequency and percentage for categorical variables, and mean and SD for continuous variables. To conduct a matched case-control analysis for continuous variables, we used a linear multilevel

model to compare the mean scores of IQ, the SNAP-IV, the CANTAB test, the GFA, and LI values of the four pairs of frontostriatal tracts between the ADHD and typically developing groups. For the GFA values, a general linear model analysis for repeated measures was used with the sides (left and right hemispheres) and tracts (dorsolateral, medial prefrontal, orbitofrontal, and ventrolateral) as the within-subject variables and groups (ADHD and typically developing) as the between-subject variable. Then the post hoc analysis was performed using the paired t-test (two-tailed) to compare the differences in the GFA values of dorsolateral, medial prefrontal, orbitofrontal, and ventrolateral tracts within the same subjects. To control for inflation of type I error in calculating multiple univariate correlations, multiple linear regression models with the backward elimination procedure were conducted to find the relationship between the measures of executive function and the GFA measures of the four pairs of bilateral frontostriatal tracts (dorsolateral, medial prefrontal, orbitofrontal, and ventrolateral). The GFA values of the 8 frontostriatal tracts were entered as independent variables, and ADHD symptoms based on the SNAP-IV and each of the performance scores on the CANTAB tasks, as the dependent variables. We used backward elimination procedure to identify the fitted model containing the variables from 8 frontostriatal tracts which maintained significant effects on each of CANTAB measures. The R^2 value provided a quantitative measure of how well the fitted model with frontostriatal tracts predicted the CANTAB measures.

Results

Children with ADHD had significantly lower GFA values than typically developing children in four pairs of frontostriatal tracts (Cohen's *d*, 0.88 ~ 1.54). Children with ADHD did not demonstrate significant left-to-right asymmetry in the dorsolateral and medial prefrontal pairs as shown in typically developing children and

had lower LI of the medial prefrontal ($d = 0.53$; $P = 0.047$) and dorsolateral ($d = 0.57$; $P = 0.051$) tracts than typically developing children.

The multiple linear regression with backward elimination analysis revealed that the GFA value of the right orbitofrontal tract significantly associated with inattention, and GFA of the left dorsolateral and right medial prefrontal fiber tracts significantly associated with hyperactivity/impulsivity within the ADHD group. Within the ADHD group, results showed (1) that left orbitofrontal and left ventrolateral GFA values were significantly associated with IED total errors (adjusted) and IED total trials (adjusted); (2) that left orbitofrontal GFA was significantly associated with RVP probability of false alarm and RVP B" (right ventrolateral GFA, too); (3) that left orbitofrontal GFA was significantly associated with SWM total errors; (4) that right and left dorsolateral GFA values were significantly associated with SOC problems solved in minimum moves and SOC mean initial thinking time; and (5) that left dorsolateral GFA was significantly associated with SOC mean subsequent thinking time.

Discussion

With the strengths of using tractography-based analysis, complete assessments of clinical symptoms and executive function, and a matched case-control study design with matching at the individual level, we found that children with ADHD had disturbed microstructural integrity of all four pairs of frontostriatal tracts, and that clinical symptomatology and executive functions correlated with integrity of the frontostriatal tracts, particularly left orbitofrontal and ventrolateral fiber tracts. Our findings lend evidence to support that disturbed frontostriatal integrity might be responsible for the clinical symptoms of and executive dysfunction in ADHD.

Reduced white matter integrity of all the frontostriatal tracts in ADHD are consistent with previous DTI studies (Ashtari et al., 2005; Pavuluri et al., 2009),

suggesting frontostriatal integrity changes may be the structural correlates for ADHD. Low GFA values may reflect axonal degeneration, or a less well-organized tract (Mori & Zhang, 2006). To our best knowledge, this is the first study that demonstrates a direct association between frontostriatal microstructural integrity, mainly the orbitofrontal and ventrolateral fiber tracts, and executive functions measured by the CANTAB in children with ADHD and typically developing children as well.

Our findings should be interpreted in the context of some limitations. First, a cross-sectional study design has prevented us from determining whether the white matter abnormalities observed in these frontostriatal tracts reflect the primary pathophysiology of ADHD or are the consequences of a compensatory neuro-developmental process. Second, the present study only focused on the frontostriatal tracts. Exploration of frontotemporal (A. Konrad et al., 2010) and fronto-striato-parieto-cerebellar (Rubia et al., 2009) networks, which may be associated with executive dysfunction in ADHD, is warranted. Third, we cannot completely exclude any potential long-term effects of the medication on microstructural integrity of the frontostriatal tracts given that 18 children with ADHD had taken medication for treating ADHD at least one week before the scan. Fourth, due to the matched design, we were not able to study the age effect in the whole sample. It merits further investigation to clarify the developmental trajectory of the microstructural integrity of the frontostriatal and other tracts using a longitudinal study design.

Implication

Combining previous DTI studies and our DSI tractography analysis, there is strong evidence to support disturbed white matter tract integrity of the four frontostriatal circuits (i.e., dorsolateral-caudate, medial prefrontal-caudate,

orbitofrontal-caudate, and ventrolateral-caudate) in children with ADHD, and associations between integrity of the frontostriatal tracts and measures of ADHD symptoms in children with ADHD and executive functions in children with ADHD and typically developing children as well. Further imaging genetics research on the relationship between frontostriatal circuitry, executive function, and candidate genes is warranted.

6.4 Genetic association studies on ADHD

6.4.1 Association of *DAT1* gene and ADHD

Introduction

Several lines of evidence point to the potential importance of the *DAT1* gene in the pathophysiology of ADHD. First, methylphenidate, the most widely used stimulant for ADHD treatment, inhibits the action of DAT, thereby increasing synaptic dopamine concentration to achieve the therapeutic effects (Volz, 2008). Second, previous neuroimaging studies have also suggested the involvement of DAT in ADHD (Cheon et al., 2003). Third, after 3 months of treatment with methylphenidate in children with ADHD, a down-regulation of the DAT with a maximum of 74.7% has been observed in the striatal system (Vles et al., 2003). Fourth, the *DAT1* knock-out (KO) mice represent an appropriate animal model for ADHD to elucidate the underlying neural basis of this disorder. The *DAT1* KO mice exhibited marked hyperactivity, and this activity was exacerbated by exposure to a novel environment (Gainetdinov et al., 1999).

A possible explanation for the inconsistencies of the *DAT1* gene in ADHD is that a combination of susceptibility variants across the gene exists and these combinations

differ across distinct populations (Genro et al., 2008). Thus, simply genotyping one marker per gene will provide little conclusive evidence for association of that gene with the disease. While numerous SNPs have been identified in the *DAT1* gene, a relevant question is to determine which of these SNPs should be tested to detect an association with ADHD. Genetic studies using markers chosen at random from polymorphic sites may not be reliable for the detection of nearby causal variation. Association studies require that SNPs be selected to maximize the probability that significant LD exists between the unknown causative mutation and the markers genotyped in studies. Genetic analyses using haplotype-tagging SNP approaches allow for a more complete examination of how polymorphisms in specific genes may be associated with ADHD (Kollins et al., 2008). These methods aim to improve efficiency by removing redundant genotyping and gather additional association information via LD.

Taken together, although the *DAT1* gene was implicated in the pathogenesis of ADHD, significant heterogeneity was present across studies and no conclusion can be drawn about the association in any single ethnicity (Cheuk et al., 2006). More studies are needed in each ethnicity before a firm conclusion can be made. As Han Chinese is the largest population in the world, further studies are needed to determine if there is a relationship between ADHD and *DAT1* gene. Using a haplotype-tagging SNP approach, we performed a family-based study to investigate the genetic associations between the *DAT1* gene and ADHD and its diagnostic subtypes in our local Han Chinese population in Taiwan to establish a role of *DAT1* gene in the etiology of this disorder.

Materials and Methods

The probands were 273 Han Chinese children with ADHD, who were recruited

consecutively from the Children's Mental Health Center, National Taiwan University Hospital, Taiwan. Families of probands were also recruited, resulting in 906 subjects in total. There were 108 families with one proband, one sibling, and two parents; 9 families with one proband, two siblings, and two parents; 110 trios (one proband plus two parents); 7 families with one proband, one sibling, and one parent; and 39 duos (one proband plus one parent). The probands were predominantly male (85.7%) and their mean age was 10.8 (SD = 2.5) years. Most of them presented the combined subtype (65.2%), followed by the inattentive (28.9%) and hyperactive/impulsive (5.9%) subtypes. Among 133 siblings (male 41.5%; mean age, 11.5±3.8), 58 (43.6%) were suspected of ADHD based on the Chinese K-SADS-E (inattentive subtype, 51.7%; combined subtype, 25.9%; hyperactive/impulsive subtype, 22.4%).

Tag SNPs were selected by searching Han Chinese data from the HapMap project (www.hapmap.org) using the Tagger program. The following criteria were used to identify tag SNPs: (1) SNPs were located in the *DAT1* gene; (2) SNPs had a minor allele frequency (MAF) $\geq$ 0.10; and (3) the other unselected SNPs could be captured by one of the tag SNPs with an LD correlation coefficient (r^2) $\geq$ 0.80. SNP selection was completed in September, 2008. In total, 14 tag SNPs (rs2937639, rs2617605, rs393795, rs10052016, rs37020, rs40358, rs37022, rs466630, rs27048, rs429699, rs11133767, rs40184, rs1042098, rs27072) were identified. In addition, we selected other 4 SNPs (rs6350, rs403636, rs463379, rs6347) based on relevance in the literature.

All SNP genotypings were performed by the method of matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS). The VNTR in the 3'UTR of the *DAT1* gene was amplified using the primers: forward, 5'-TGTGGTGTAGGGAACGGCCTGAG, and reverse, 5'-CTTCCTGGAGGTCACGGCTCAAGG. PCR product with various sizes ranging

from 323 bp (6 repeats) to 523 bp (11 repeats) were electrophoresed in 3.5% agarose gel to visualize the repeat number.

The quality of genotyping data were checked on indicators of Hardy-Weinberg equilibrium (HWE), using Haploview version 4.0. We used Haploview software to construct haplotype blocks constituted by strong LD markers. We used the Family-Based Association Test (FBAT) software version 2.0.2 to conduct data analysis. This program used data from nuclear families, siblings, pedigrees, or any combination and provided unbiased tests with or without founder genotypes. The FBAT empirical variance option (FBAT -e) was used for testing association in an area of known linkage with multiple siblings in a family. Haplotype analyses were performed using the Haplotype-Based Association Test (HBAT) in the FBAT program. HBAT –p option (which used the full conditional distribution of offspring haplotypes) was used to compute an "exact" P value via a Monte Carlo method for each haplotype separately and for the minimum observed P value among the haplotypes. Because of the small number of probands with the hyperactive/impulsive subtype, separate analyses were not performed for this subtype.

Results

A total of 19 polymorphisms (18 SNPs and the 3'VNTR) were investigated here to cover a region of 50kb in the *DAT1* gene. An SNP was included in the analysis if the genotype missing rate was lower than 30%. Accordingly, four SNPs (rs6350, rs10052016, rs6347, and rs11133767) were excluded from further analysis. All the remaining 14 SNP markers and the 3'VNTR were compatible with the Hardy-Weinberg equilibrium distribution. Observation of D′ values indicated three main haplotype blocks (HBs): HB1 covering 19kb and including the variants of introns 2, 4 and 6; HB2 covering 3kb and including the variants of introns 8 and 11;

and HB3 covering 953bp and including the variants of 3′UTR.

For ADHD inattentive subtype, one SNP showed biased transmission for ADHD children: rs429699 T allele (P = 0.017). After adjustment for multiple testing, the corrected P value did not remain significant. One SNP (rs40184, P = 0.081) and the 10-repeat allele of 3′UTR (P = 0.061) displayed trends for association. Haplotype analyses revealed an overtransmitted haplotype rs27048 (C) /rs429699 (T) in HB2 in the inattentive subtype (P= 0.008). This haplotype contained the SNP (rs429699) that was nominally significant when considered on its own. Permutation test for this CT haplotype showed that association with the inattentive subtype subsample remained significant (2-sided P = 0.006; the smallest observed P = 0.022). The SNP rs429699 that was nominally significant for inattentive subtype also showed nominally significant association with the inattention severity (P= 0.019). The haplotype rs27048 (C) /rs429699 (T) that was significant for the inattentive subtype also demonstrated significant association with the inattention severity (P= 0.012).

Discussion

To our best knowledge, this is the first study on the genetics of ADHD to describe the architecture of LD across the *DAT1* gene in the Han Chinese population, and our results highlight the necessity of characterizing the *DAT1* gene for association studies, and choosing a subset of sites that are representative of the LD structure of variation in this gene. Our findings provided evidence for a role of the *DAT1* gene in ADHD, primarily with respect to the inattentive subtype, in both SNP (rs429699) and haplotype (rs27048 (C) /rs429699 (T)) analyses. Quantitative analyses also revealed positive association between the haplotype rs27048/rs429699 and inattention severity. The findings not only support that *DAT1* is a susceptibility gene primarily for the inattentive subtype of ADHD (Krause et al., 2003) but also suggest the association of

DAT1 gene with the inattentive symptoms based on DSM-IV (K. Konrad et al., 2010).

In addition to *DAT1* gene, previous studies have shown the effects of other candidate

genes on the inattentive ADHD subtype. For example, a haplotype block

encompassing the 5HT1B receptor gene (Smoller et al., 2006) and a polymorphism at

the alpha-2a-adrenergic receptor gene (Schmitz et al., 2006) were associated with

inattentive subtype.

Although the present study shows that the *DAT1* gene is a susceptibility locus for

the inattentive subtype of ADHD, no direct functional effects of these polymorphisms

have been examined and identified. Thus, the causal variants remain to be established.

The *DAT1* gene is expressed primarily in brain areas with dopaminergic circuitry,

such as mesostriatal, mesolimbic, and mesocortical pathways (Ciliax et al., 1999), and

this highly restricted pattern of *DAT1* gene expression is presumably regulated by a

unique combination of regulatory factors. Although intronic polymorphisms have no

direct effect on the amino acid sequence, there are a growing number of examples of

intronic sequences that play an important role in the tissue-specificity of *DAT1* gene

expression (Greenwood & Kelsoe, 2003). Future studies are needed to identify

intronic variants of the *DAT1* gene causally related to the ADHD inattentive subtype.

Our findings should be interpreted in the context of some limitations. First, the

number of individuals with the subtypes of ADHD was relatively small in the present

study. Although our findings show significant association with *DAT1* gene in the

predominantly inattentive ADHD subtype, the power to detect loci of modest effect

would be correspondingly lower for subtype analyses. A larger sample is needed for

stronger evidence of association with the markers at the *DAT1* locus. Second, only

one gene was examined in our study. For complex disorders, analyses of different

genes involved in the pathophysiology of ADHD may enhance our understanding on

the genetic contributions to the etiology of this disorder, and therefore gene-gene

interactions should be considered in further research. Third, ADHD may be accounted for by both genetic and environmental factors. Further studies are required to detect the effect of interaction between candidate genes and environmental factors on this disorder. Fourth, the probands in the current study were clinic-referred, and thus they represented the upper ends of ADHD-related symptoms. It is needed to test whether our findings could be extended to the general population.

Implication

In summary, our analyses identified an association between a haplotype of *DAT1* gene and the inattentive subtype of ADHD, supporting the relevance of the dopaminergic system in the pathophysiology of ADHD, especially in the dimension of inattention. Single marker analyses within this haplotype block also demonstrated nominal association with the inattentive subtype. The focus on the complete gene plus the use of haplotype mapping with LD structure in association studies of ADHD may help to better understand and interpret the results in the *DAT1* gene for ADHD genetics. Because significant ADHD-*DAT1* association can only be detected with the inattentive subtype sample, our findings highlight the importance of establishing genetically homogeneous samples for ADHD molecular genetic studies. To enhance our understanding on the role of *DAT1* gene, more biological studies are needed to examine the effects of different polymorphisms on the *DAT1* gene and protein functions, and to determine whether variants at this gene causally related to ADHD and the inattentive dimension can be identified.

6.4.2 Association of *DAT1* gene and executive dysfunction in ADHD

Introduction

It has been proposed that use of endophenotypes relevant to ADHD is likely to be informative and allow for increased detection of genetic effects (Castellanos & Tannock, 2002). Because previous studies in Western countries (D. I. Slaats-Willemse et al., 2007) and in Taiwan (Gau & Shang, 2010a) have provided strong evidence to support that executive function can be a useful cognitive endophenotype for ADHD, examining the relationship between the candidate genes and executive function may provide insight into the pathways leading from genes to ADHD. Given the well-established neuromodulatory influence of the dopamine over executive function, several lines of evidence point to the potential importance of the *DAT1* gene in executive function. First, the *DAT1* knock-out (KO) mice represent an appropriate animal model for ADHD to elucidate the underlying neural basis of this disorder. The *DAT1* KO mice display impairments in executive function (B. Li et al., 2010) Second, methylphenidate, one of the main drugs used to treat ADHD, targets the dopamine transporter (DAT). Much research has found that methylphenidate was associated with better executive function performance in children with ADHD (Vance et al., 2003). Third, previous studies have documented the role of the *DAT1* gene in the development of executive attention network in healthy children (Rueda et al., 2005). Fourth, imaging genetic studies have shown that the neural response to working memory load varied by the genetic variants of the *DAT1* gene in typically developing children (Stollstorff et al., 2010).

Previous studies exploring executive function in relation to *DAT1* in ADHD have focused on the variable number of tandem repeat (VNTR) polymorphism in 3´-untranslated region (3'UTR), and the results revealed a mixed picture (Barkley et al., 2006; Karama et al., 2008). Several indices of executive function (digit span and the Tower of London) appeared to be modulated by the 3' VNTR of *DAT1* (Karama et al., 2008). Children with ADHD and homozygous for 10-repeat allele showed

impaired performance on selective attention and response inhibition compared with heterozygotes (Cornish et al., 2005). However, contrary findings have been also reported, in which ADHD patients with the 10-repeat allele performed better than those with the 9-repeat allele (Boonstra et al., 2008). In addition, no association has also been found between the 3' VNTR and executive function measured by the Wisconsin Card Sorting Task (Barkley et al., 2006) and the Stroop Color-Word test (Loo et al., 2008) in children with ADHD. Methodological aspects, including differences in ADHD measurement methods, participants' characteristics, and neuropsychological tasks employed, may contribute significantly to the inconsitent pattern of results. In addition, because a combination of susceptibility variants across the gene exists, it may be the combination of certain risk genotypes rather than one single risk genotype that leads to presence of cognitive dysfunction (Mill et al., 2006).

Taken together, significant heterogeneity is present across studies and no conclusion can be drawn about the association. More studies are needed before a firm conclusion can be made. As Han Chinese is the largest population in the world, further studies are needed to determine if there is a relationship between the *DAT1* gene and executive dysfunction in ADHD. Using a haplotype-tagging SNP approach, our previous work has confirmed the association between polymorphisms in *DAT1* and ADHD diagnosis in the Han Chinese population in Taiwan (Shang et al., 2011). In this study, we further extended our sample size with 382 families (n = 1298) to investigate the genetic associations between the *DAT1* gene and executive dysfunction in probands with ADHD and their family members.

Materials and Methods

The probands were 382 Han Chinese children with ADHD, who were recruited consecutively from the Children's Mental Health Center, National Taiwan University

Hospital, Taiwan.

Families of probands were also recruited, resulting in 1298 subjects in total. There were 164 families with one proband, one sibling, and two parents; 15 families with one proband, two siblings, and two parents; 144 trios (one proband plus two parents); 17 families with one proband, one sibling, and one parent; and 42 duos (one proband plus one parent). The probands were predominantly male (86.1%) and their mean age was 10.5±2.6 years. Most of them presented the combined subtype (67.3%), followed by the inattentive (27.0%) and hyperactive/impulsive (5.7%) subtypes. Among the 211 siblings (male 43.6%; mean age, 11.4±3.9) in our sample, 57 were suspected of ADHD based on the Chinese K-SADS-E (inattentive subtype, 50.9%; combined subtype, 28.1%; hyperactive/impulsive subtype, 21.0%).

Four tasks of the CANTAB involving executive abilities were employed in this study, including SSP, SWM, IED, and SOC. All SNP genotypings were performed by the method of matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS). The VNTR in the 3'UTR of the *DAT1* gene was genotyped using the PCR and electrophoresis. We performed association analysis for the ADHD families on the quantitative scores of executive function as measured with the SSP, SWM, IED, and SOC using the FBAT and HBAT programs with the additive model of inheritance.

Results

Observation of D´ values indicated three main haplotype blocks (HBs): HB1 covering 19kb and including the variants of introns 2, 4 and 6; HB2 covering 3kb and including the variants of introns 8 and 11; and HB3 covering 660bp and including the variants of 3´UTR. We then tested for association between *DAT1* genotypes and quantitative scores of executive function as measured with the SSP, SWM, IED, and

SOC. We found associations for rs2937639 and SWM within errors ($P = 0.049$); for rs2617605 and SWM within-search errors ($P = 0.004$), SWM within-search errors 8 boxes ($P = 0.007$), SWM double errors ($P = 0.002$), and SWM double errors 8 boxes ($P = 0.009$); for rs403636 and SWM double errors ($P = 0.024$); for rs37020 and SWM double errors ($P = 0.004$) and SWM double errors 8 boxes ($P = 0.033$) (Table 3). The association between rs2617605 and SWM double errors survived the correction of alpha level for multiple testing.

Haplotype analyses revealed an overtransmitted haplotype rs403636 (G) /rs463379 (C) /rs393795 (C) /rs37020 (G) in HB1 for SWM within-search errors ($P = 0.0005$), SWM within-search errors 8 boxes ($P = 0.001$), SWM double errors ($P = 0.0007$), and SWM double errors 8 boxes ($P = 0.002$) (Table 4). This haplotype contained the two SNPs (rs403636 and rs37020) that were nominally significant when considered on their own. Permutation test for this GCCG haplotype showed that associations remained significant for SWM within-search errors (2-sided $P = 0.0003$; the smallest observed $P = 0.001$), SWM within-search errors 8 boxes (2-sided $P = 0.0003$; the smallest observed $P = 0.002$), SWM double errors (2-sided $P = 0.0004$; the smallest observed $P = 0.001$), and SWM double errors 8 boxes (2-sided $P = 0.0007$; the smallest observed $P = 0.004$).

No allele or haplotype was significantly associated with the scores of SSP, IED, SOC, and strategy utilization in SWM.

Discussion

In the present study, we tested the association between *DAT1* on four executive functioning tasks that were promising endophenotypes for ADHD. Our findings report novel associations between a haplotype rs403636 (G) /rs463379 (C) /rs393795 (C) /rs37020 (G) of the *DAT1* gene and performance on the SWM task that survived

corrections for multiple comparisons. The current study provides evidence that allelic variation in the *DAT1* gene accounts for significant variance in neuropsychological indices of spatial working memory.

Our findings provided some insight into the effects of the *DAT1* gene on the spatial working memory in ADHD. Spatial working memory, one of the major executive functions, seems to be mediated by a complex network of brain structures including the prefrontal cortex (PFC) (van Asselen et al., 2006), posterior parietal cortex (PPC) (Koch et al., 2005), and to a lesser extent, hippocampus (Abrahams et al., 1999). In a study to examine the neural correlates of various aspects of spatial working memory in a group of stroke patients, damage to the right dorsolateral PFC and right PPC impaired the ability to keep spatial information on-line, as indicated by the within-search errors (van Asselen et al., 2006). Moreover, patients with damage to the right dorsolateral PFC, right PPC, and the hippocampal formation bilaterally made more between-search errors (van Asselen et al., 2006). Although *DAT1* is mainly expressed in the striatum and to a lesser extent in the PFC, PPC, and hippocampus (Diamond, 2007), several lines of evidence suggest that the influence of *DAT1* on spatial working memory is mediated by the striatum and its cortical projections. First, DAT availability in the caudate is associated with activation in the parietal cortex during spatial attention (Tomasi et al., 2009). Landau et al. have found that caudate dopaminergic function is related to PFC-dependent functions, particularly brain activation and behavioral performance during working memory tasks (Landau et al., 2009). Second, higher accuracy in the performance on working memory tasks engaged prefrontal-striatal-parietal regions (Stollstorff et al., 2010). Third, functional magnetic resonance imaging studies have found that parietal activation during tasks tapping processes of working memory vary by *DAT1* genotype (Stollstorff et al., 2010). Polymorphisms in the *DAT1* gene are associated with neuronal activity in the

working memory cortical network, including the PFC (Bertolino et al., 2006; Bertolino et al., 2009). Thus, these results may imply that prefrontal and parietal activation is sensitive to *DAT1* allelic differences during working memory tasks. For a full understanding of the underlying mechanism, our next step is to examine genetic effects on the relationship between spatial working memory and brain activation in patients with ADHD.

Although an effect of *DAT1* on spatial working memory was demonstrated in the present study, we failed to find evidence for association between allelic variations in the *DAT1* gene and performance on other measures of executive function, such as spatial span, attentional set-shifting, and spatial planning. This might be related to subtle differences in the underlying neurotransmitter pathways mediating the executive functions. Several studies have found attentional set-shifting appeared to be modulated by dopamine-related genes, such as *DBH* (Barkley et al., 2006) and *COMT* (Schulz et al., 2011). However, previous studies failed to found associations of *DAT1* with measures of performance on the set-shifting tasks (Barkley et al., 2006). Schulz et al. suggest that while prefrontal dopamine turnover seems to modulate performance in set-shifting, striatal dopamine turnover mediated by *DAT1* polymorphisms seems less important in this regard (Schulz et al., 2011). In regard to associations of *DAT1* with spatial planning, inconsistent results have been yielded (Karama et al., 2008). Our current findings need replication before firm conclusions can be drawn on the specificity of *DAT1* in relation to spatial working memory.

Our findings should be viewed in the light of several limitations. First, only one gene was examined in our study. Analyses of different genes involved in the pathophysiology of spatial working memory in patients with ADHD may enhance our understanding on the genetic contributions to the etiology of this disorder. Second, the probands in the present study were clinic-referred, and thus they represented the upper

ends of ADHD-related symptoms. It is needed to test whether our findings could be extended to the general population. Third, the neuropsychological measures used in the present study are by no means of the full domain of cognitive functions relevant for ADHD. Our findings need replication before firm conclusions may be drawn on the effects of *DAT1* on neuropsychological functioning in patients with ADHD.

Implication

In summary, the present study has provided strong evidence that DNA variation in the *DAT1* gene predicts measures of spatial working memory. The association found between *DAT1* and spatial working memory may help to increase our understanding of how this gene contributes to ADHD susceptibility because spatial working memory is one of the main deficits and an important endophenotype of ADHD. Our findings support that cognitive endophenotype may be an important tool to understand the genetics of ADHD, given their more direct link to the genetic etiology of this disorder.

7. 參考文獻

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8. 表與圖 (Tables and Figures)

表 1 (Table 1)： 神經認知功能障礙研究中 ADHD 患者與對照組的人口學特質

	ADHD (n = 53)	對照組 (n = 53)
參加研究時的年齡 (平均 ± 標準差)	12.7 ± 1.4	12.7 ± 1.2
男性百分比	75.5	75.5
出現明顯 ADHD 症狀的年齡 (平均 ± 標準差)	4.8 ± 1.7	--
被診斷為 ADHD 的年齡 (平均 ± 標準差)	7.6 ± 2.9	--
被診斷與本研究追蹤之間的期間 (年)	5.0 ± 3.1	--
目前使用 ADHD 藥物的百分比	60.4	--
曾經使用 ADHD 藥物的百分比	83.0	--
使用 methylphenidate 的期間 (月)	28.4 ± 24.9	--
與父母同住的百分比	90.4	92.9
父親教育程度 (百分比)		
大專及以上	62.8	62.5
高中	23.5	29.2
國中及以下	13.7	8.3
父親職業 (百分比)		
專業人員	22.9	24.4
技術人員	77.1	73.2
非技術人員	0.0	2.4
母親教育程度 (百分比)		
大專及以上	50.0	56.5
高中	38.5	32.6
國中及以下	11.5	10.9
母親職業 (百分比)		
專業人員	4.2	2.4
技術人員	60.4	73.2
非技術人員	35.4	24.4

表 2 (Table 2)： 青少年時期的精神科診斷

精神科診斷	ADHD (n = 53) N	(%)	對照組 (n = 53) N	(%)	OR	95% CI		p
對立反抗性疾患	39	(73.6)	10	(18.9)	6.80	(2.66	17.39)	<0.001
行為規範障礙疾患	16	(30.2)	2	(3.8)	14.99	(1.98	113.47)	0.009
情感性疾患	10	(18.9)	6	(11.3)	1.67	(0.61	4.59)	0.323
憂鬱疾患	5	(9.4)	6	(11.3)	0.83	(0.25	2.73)	0.763
雙極性情感疾患	5	(9.4)	0	(0.0)	--	--	--	0.028[a]
焦慮疾患	22	(41.5)	11	(20.8)	2.57	(1.07	6.16)	0.034
特定畏懼症	17	(32.1)	5	(9.4)	5.00	(1.45	17.27)	0.011
其它焦慮疾患	11	(20.8)	4	(7.6)	3.33	(0.92	12.11)	0.067
廣泛性焦慮疾患	3	(5.7)	0	(0.0)	--	--	--	0.121[a]
社交畏懼	7	(13.2)	2	(3.8)	6.00	(0.72	49.79)	0.097
分離焦慮疾患	3	(5.7)	1	(1.9)	3.00	(0.31	28.84)	0.341
恐慌疾患	3	(5.7)	1	(1.9)	3.00	(0.31	28.84)	0.341
懼曠症	1	(1.9)	0	(0.0)	--	--	--	0.500[a]
強迫症	2	(3.8)	2	(3.8)	1.00	(0.14	7.10)	1.000
睡眠疾患	21	(39.6)	10	(18.9)	3.75	(1.25	11.30)	0.019
抽搐疾患	4	(7.6)	2	(3.8)	2.00	(0.37	10.92)	0.424
物質使用疾患	1	(1.9)	0	(0.0)	--	--	--	0.500[a]
飲食障礙疾患	3	(5.7)	0	(0.0)	--	--	--	0.121[a]

縮寫：OR = 勝算比, CI = 信賴區間

[a] Fisher's 檢定.

表 3 (Table 3)： 執行功能測驗表現之比較

	ADHD		對照組				Cohen's *d*
	平均值	(標準差)	平均值	(標準差)	F	*p*	
Spatial Span							
Span Length	6.79	(1.52)	7.06	(1.39)	0.87	0.356	0.19
Total Error	15.02	(7.32)	14.31	(6.63)	0.29	0.590	0.10
Total Usage Error	2.32	(1.46)	1.75	(1.27)	5.10	0.028	0.42
Spatial Working Memory							
Strategy Utilization	33.89	(4.76)	33.19	(3.67)	0.71	0.402	0.16
Total Errors	30.38	(19.41)	20.04	(13.91)	9.94	0.003	0.61
# of Errors: 4-box problems	0.81	(1.47)	0.57	(1.29)	0.90	0.347	0.17
# of Errors: 6-box problems	8.43	(7.47)	5.34	(5.71)	5.74	0.020	0.46
# of Errors: 8-box problems	21.13	(12.93)	14.13	(9.41)	10.15	0.002	0.62
Intra-dimensional & Extra-dimensional Shift							
Complete Stages	8.55	(1.12)	8.68	(0.73)	0.52	0.475	0.14
Complete Stage Trials	79.49	(19.74)	72.57	(13.62)	4.42	0.041	0.41
Pre-extra-dimensional Shift Errors	8.51	(5.87)	6.98	(3.23)	2.90	0.095	0.32
Extra-dimensional Shift Errors	8.72	(9.70)	8.53	(9.70)	0.01	0.921	0.02
Stocking of Cambridge							
Problems Solved in Minimum Moves	7.89	(1.89)	8.55	(1.70)	4.36	0.042	0.37
Mean Moves: Total Moves	17.87	(1.79)	17.18	(1.84)	4.45	0.040	0.38
2-move problem	2.01	(0.07)	2.00	(0.00)	1.00	0.322	0.20
3-move problem	3.25	(0.41)	3.21	(0.35)	0.26	0.612	0.10
4-move problem	5.65	(1.11)	5.40	(1.05)	1.68	0.200	0.23
5-move problem	7.10	(1.57)	6.58	(1.31)	3.46	0.069	0.36
Mean Initial Thinking Time(ms)							
Total initial thinking time	3800.91	(2539.52)	4953.12	(3305.08)	4.05	0.049	0.39
2-move problem	1194.38	(778.00)	1393.75	(999.90)	1.31	0.257	0.22
3-move problem	3147.47	(2877.39)	4235.14	(4072.45)	2.52	0.118	0.31
4-move problem	4725.33	(4204.48)	6056.42	(4873.64)	2.27	0.138	0.29
5-move problem	6162.79	(6335.71)	8127.17	(7016.33)	2.26	0.139	0.29
Mean Subsequent Thinking Time(ms)							
Total subsequent thinking time	443.05	(370.64)	688.91	(723.36)	5.13	0.028	0.43
2-move problem	90.37	(171.34)	221.51	(530.85)	2.93	0.093	0.33
3-move problem	206.14	(426.25)	212.11	(379.50)	0.01	0.940	0.01
4-move problem	882.67	(934.39)	1353.41	(1973.81)	2.61	0.112	0.30
5-move problem	567.48	(560.53)	968.61	(1238.12)	4.54	0.038	0.42

表 4 (Table 4)： ADHD 患者、未發病手足、以及對照組之人口學特質

	ADHD (N=279)	手足(N=108)	對照組 (N=173)	
	平均值(標準差) or %	平均值(標準差) or %	平均值(標準差) or %	F 或 χ^2
評估時的年齡	12.5 (1.6)	12.5 (3.4)	12.6 (1.5)	0.06
男性 %	85.7	40.7	72.8	79.79***
男女比	6.0	0.69	2.7	
目前使用 methylphenidate	50.9			
使用 methylphenidate 的期間（月）	20.1 (22.1)			4.31
智商	103.0 (11.6)	103.0 (10.6)	110.7 (9.5)	29.97***
母親				
年齡	42.7 (4.2)		43.6 (3. 9)	4.84*
教育程度				
大專及以上	50.6		63.9	7.16*
高中	40.0		29.7	
國中及以下	9.4		6.4	
職業狀態				
專業人員	4.1		6.2	4.09
技術人員	59.3		66.4	
其它	36.7		27.4	
父親				
年齡	45.7 (4.8)		46.2 (4.5)	1.07
教育程度				
大專及以上	59.9		76.0	11.41**
高中	29.6		18.4	
國中及以下	10.5		5.7	
職業狀態				
專業人員	14.8		20.6	2.24
技術人員	79.9		74.0	
其它	5.3		5.5	

p<0.05; ** *p*<.01; *** *p*<.001.

表 5 (Table 5)： ADHD 患者、未發病手足、以及對照組目前精神科診斷

精神科診斷	ADHD (N = 279)		手足 (N = 108)		對照組 (N = 173)		OR (95% CI) or *p**		
	N	(%)	N	(%)	N	(%)	ADHD vs.對照組	手足 vs.對照組	ADHD vs.手足
注意力不足過動症	250	(89.6)	0	(0)	0	(0)	—	—	—
混合型	102	(36.6)	0	(0)	0	(0)	—	—	—
注意力不足亞型	121	(43.4)	0	(0)	0	(0)	—	—	—
過動衝動亞型	27	(9.7)	0	(0)	0	(0)	—	—	—
對立反抗性疾患	155	(55.6)	12	(11.1)	12	(6.9)	17.19(9.05-32.64)	1.75(0.75-4.11)	9.80(5.09-18.87)
行為規範障礙疾患	54	(19.4)	4	(3.7)	2	(1.2)	20.80(4.92-88.00)	3.42(0.60-19.40)	6.08(2.12-17.47)
焦慮疾患	77	(27.6)	32	(29.6)	33	(19.1)	1.63(1.02-2.62)	1.80(1.01-3.20)	0.91(0.55-1.50)
情感性疾患	36	(12.9)	7	(6.5)	7	(4.0)	3.54(1.53-8.23)	1.64(0.55-4.88)	2.16(0.92-5.05)
憂鬱疾患	28	(10.0)	5	(4.6)	7	(4.0)	2.67(1.13-6.31)	1.15(0.35-3.77)	2.32(0.86-6.24)
雙極性情感疾患	8	(2.9)	2	(1.9)	0	(0)	0.024*	0.072*	0.566*
抽搐疾患	18	(6.5)	1	(0.9)	3	(1.7)	3.94(1.13-13.78)	0.55(0.06-5.51)	7.16(0.92-55.65)

* Fisher 檢定.

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表 6 (Table 6)： ADHD 患者、未發病手足、以及對照組之執行功能測驗表現的比較

變項 平均值(標準差)	ADHD (N=279)	手足 (N=108)	對照組 (N=173)	單變項分析 F	比較	多變項分析† F	比較	β	Cohen's d A vs. S	A vs. C	S vs. C
Digit Span (Verbal Executive Functioning)											
Digit span, forward	8.28 (0.96)	8.37 (0.89)	8.50 (0.79)	3.48*	A<C	7.01**	A<S,C	-0.11**	0.10	0.25	0.15
Digit span, backward	5.29 (1.69)	5.50 (1.61)	6.08 (1.58)	11.93***	A,S<C	9.09***	A<C	-0.39***	0.13	0.48	0.36
Intradimension/Extradimension Shift											
Trials of completed stages	76.49 (19.98)	73.15 (17.06)	73.84 (15.23)	1.87	-	1.27	-	1.42	-0.18	-0.15	0.04
Extra-dimensional shift errors	11.20 (10.34)	12.20 (10.65)	8.78 (9.32)	4.46*	A,S>C	1.94	-	1.08*	0.10	-0.25	-0.34
Pre-extra-dimensional shift errors	7.84 (4.70)	7.35 (3.68)	6.92 (3.89)	3.00	-	0.48	-	0.48*	-0.12	-0.21	-0.11
Completed stages	8.40 (1.02)	8.34 (1.00)	8.63 (0.87)	3.86*	A<C	1.62	-	-0.11*	-0.06	0.24	0.31
Total errors	23.45 (13.29)	22.04 (12.39)	18.38 (11.40)	8.72***	A>C	4.52*	A>C	2.47***	-0.11	-0.41	-0.31
Total errors(adjusted)	30.26 (24.89)	30.14 (23.47)	22.71 (21.97)	5.62**	A>C	2.21	-	3.48**	-0.00	-0.32	-0.33
Spatial Span											

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Span length	6.62 (1.49)	6.87 (1.66)	7.55 (1.30)	21.70***	A,S<C	13.78***	A<C	-0.45***	0.16	0.67	0.46
Total errors	14.28 (6.85)	12.58 (6.56)	12.91 (6.65)	3.54*	-	1.29	-	0.74*	-0.25	-0.20	0.05
Total usage errors	2.11 (1.59)	1.55 (1.50)	1.43 (1.37)	12.72***	A>S,C	4.95**	A>S,C	0.35***	-0.36	-0.46	-0.08
Spatial Working Memory											
Total errors	29.56 (17.53)	26.58 (17.66)	17.31 (13.33)	30.17***	A,S>C	18.24***	A,S>C	5.94***	-0.17	-0.79	-0.59
4 box problems	0.89 (1.60)	0.99 (1.85)	0.36 (0.95)	8.37***	A,S>C	2.70	-	0.24***	0.06	-0.40	-0.43
6 box problems	7.84 (6.30)	6.84 (6.32)	4.24 (5.15)	19.60***	A,S>C	10.69***	A>C	1.76***	-0.16	-0.63	-0.45
8 box problems	20.84 (12.03)	18.93 (12.28)	12.72 (9.56)	27.56***	A,S>C	17.63***	A,S>C	3.94***	-0.16	-0.75	-0.56
Strategy utilization	34.09 (4.59)	33.66 (4.86)	31.95 (4.66)	11.46***	A,S>C	5.43**	A>C	1.04***	-0.09	-0.46	-0.36
Stocking of Cambridge											
Problems solved in minimum moves	7.78 (2.05)	8.06 (1.93)	8.80 (1.93)	13.88***	A,S<C	5.67**	A<C	-0.49***	0.14	0.51	0.38
Total moves	18.08 (2.29)	17.57 (2.07)	16.88 (2.07)	16.26***	A,S>C	7.15*	A>C	0.59***	-0.23	-0.55	-0.33
2 move problem	2.04	2.05	2.03	0.32	-	0.30	-	0.00	0.05	-0.05	-0.09

							β	β	β	β
3 move problem	3.30 (0.57)	3.29 (0.54)	3.21 (0.44)	1.76	-	0.08	-	0.05	-0.02	-0.18	-0.16
4 move problem	5.67 (1.09)	5.49 (1.03)	5.28 (1.04)	7.06**	A>C	3.75*	A>C	0.19***	-0.17	-0.37	-0.20
5 move problem	7.14 (1.52)	6.75 (1.38)	6.36 (1.28)	16.59***	A>S,C	8.57***	A>C	0.39***	-0.27	-0.56	-0.29
Mean initial thinking time(ms)	3669.92 (2254.19)	3779.31 (2223.85)	4904.03 (2816.78)	13.47***	A,S<C	8.28***	A,S<C	-568.8***	0.05	0.48	0.44
2 move problem	1305.24 (950.36)	1221.85 (1076.20)	1379.26 (1000.46)	0.72	-	0.86	-	-30.0	-0.08	0.08	0.15
3 move problem	3413.27 (2453.87)	3129.58 (2420.21)	3578.50 (2308.79)	1.26	-	1.75	-	-49.3	-0.12	0.07	0.19
4 move problem	4890.07 (3737.23)	4358.06 (3193.88)	5990.34 (4303.43)	5.82**	A,S<C	3.66*	S<C	-414.8*	-0.15	0.27	0.43
5 move problem	5540.52 (5210.22)	6492.62 (5386.51)	8961.20 (7211.99)	17.34***	A,S<C	9.77***	A,S<C	-1652.1***	0.18	0.54	0.39

縮寫：A = ADHD；S = 未發病手足；C = 對照組；β = 線性趨勢迴歸係數

† 控制性別、年齡、智商、精神科共病、和父母教育程度

* *p*<0.05; ** *p*<.01; *** *p*<.001

表 7 (Table 7)： ADHD 患者、未發病手足、以及對照組之視覺記憶測驗表現的比較

變項	ADHD	手足	對照組	單變項分析		Cohen's *d*			多變項分析		
平均值(標準差)	(N=279)	(N=108)	(N=173)	F	比較 [b]	A-S	A-C	S-C	F	比較 [b]	β [d]
Delayed Matching to Sample											
B''[a]	-0.44(0.52)	-0.53(0.56)	-0.62(0.55)	6.30**	A>C	0.17	0.34	0.16	1.56	-	0.09***
Mean latency of correct responses(ms)											
simultaneous	3355(1004)	3180(894)	3067(745)	5.62**	A>C	0.18	0.33	0.14	0.76	-	145.11**
all delays	3554(909)	3462(862)	3580(881)	0.51	-	0.10	-0.03	-0.14	0.81	-	-5.64
Correct responses											
Total	33.00(4.05)	34.20(3.95)	35.76(2.81)	29.83***	C>S>A	-0.30	-0.79	-0.46	12.42***	S,C>A	-1.37***
simultaneous	9.56(0.79)	9.71(0.51)	9.77(0.54)	6.03**	C>A	-0.23	-0.31	-0.11	2.30	-	-0.11***
all delays	23.44(3.75)	24.49(3.76)	25.98(2.70)	28.71***	C>S>A	-0.28	-0.78	-0.46	11.80***	S,C>A	-1.26***
Probability of an error following a correct response	0.18(0.10)	0.15(0.11)	0.11(0.08)	25.21***	A>S>C	0.29	0.77	0.42	9.08***	A>C	0.03***
Probability of an error following an error response	0.15(0.16)	0.12(0.15)	0.08(0.12)	13.41***	A,S>C	0.19	0.49	0.29	4.90**	A>C	0.04***
Spatial Recognition Memory											
Percent of correct responses	82.94(10.42)	84.68(8.35)	87.37(7.48)	12.35***	C>A	-0.18	-0.49	-0.34	3.12*	C>A	-2.19***
Mean latency of correct responses(ms)	1827(535)	1924(642)	1892(614)	1.78	-	-0.16	-0.11	0.05	1.35	-	-38.08
Paired Associates Learning											
Total errors (adjusted)	5.74(6.78)	4.59(5.39)	3.43(4.06)	8.74***	A>C	0.19	0.41	0.24	1.03	-	1.15***

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Total trials (adjusted)	10.34(1.97)	9.97(2.06)	9.51(1.42)	11.00***	A>C	0.18	0.48	0.26	1.15	-	0.41***
First trial memory scores	22.08(3.10)	22.63(2.94)	23.27(2.58)	9.15***	C>A	-0.18	-0.42	-0.23	1.43	-	-0.60***
Pattern Recognition Memory											
Percent of correct responses	90.79(8.74)	91.47(8.04)	92.51(7.70)	2.31	-	-0.08	-0.21	-0.13	0.74	-	-0.85*
Mean latency of correct responses(ms)	1762(409)	1852(691)	1814(474)	2.14	-	-0.16	-0.12	0.06	3.92*	C>A	-31.30

a B": 偵測錯誤的能力

b A: ADHD; S: 未發病手足; C: 對照組

c 控制性別、年齡、智商、精神科共病、ADHD 症狀、以及父母教育程度

d β: 線性趨勢迴歸係數; *: p<0.05; **: p<.01; ***: p<.001.

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表 8 (Table 8)： ADHD 患者的人口學特質、藥物劑量、以及生命徵象

平均值 ± 標準差	ADHD (N=30)			
年齡 (範圍)	10.70 ± 1.84 (8-16)			
全智商 (範圍)	105.37 ± 13.55 (80-135)			
語言工作記憶				
順序 (z 分數)	-0.38 ± 1.33			
逆序 (z 分數)	-1.03 ± 1.02			
	用藥前	12 週	$F_{(1,29)}$	p
體重 (公斤)	38.66 ± 12.76	37.19 ± 11.88	1.08	.309
Atomoxetine 每天劑量 (毫克)	46.12 ± 14.67	46.02 ± 14.42	0.10	.756
平均劑量, 毫克/公斤/每天	1.20 ± 0.07	1.20 ± 0.08		
血壓				
收縮壓	95.58 ± 13.48	92.42 ± 17.38	0.43	.523
舒張壓	55.00 ± 8.28	55.13 ± 8.36	0.05	.820
脈搏速率	83.79 ± 11.97	90.42 ± 14.14	3.13	.097

表 9 (Table 9)： ADHD 患者的症狀在用藥前、用藥後 4 週、用藥後 12 週之比較

	用藥前	4 週	12 週	4 週 – 用藥前		12 週 – 用藥前		線性趨勢	
	平均值±標準差	平均值±標準差	平均值±標準差	平均 (95% CI)	d	平均 (95% CI)	d	β	p
GI-ADHD-S (分數 1-7)	5.57 ± 0.73	3.43 ± 0.90	2.83 ± 0.87	-2.13 (-2.53, -1.74)	-2.61	-1.37 (-1.54, -1.19)	-3.41	-1.37	<.001
NAP-IV, parent report, *T-* scores									
意力不足	79.30 ± 14.54	67.66 ± 11.02	63.28 ± 13.40	-11.62 (-16.63, -6.60)	-0.90	-8.16 (-11.00, -5.33)	-1.15	-8.20	<.001
動衝動	78.05 ± 22.30	67.73 ± 17.62	63.21 ± 13.52	-10.28 (-15.09, -5.47)	-0.51	-7.24 (-10.26, -4.21)	-0.80	-7.13	<.001
立反抗	64.37 ± 12.26	61.50 ± 10.39	58.85 ± 12.22	-2.81 (-6.79, 1.16)	-0.25	-2.77 (-4.97, -0.57)	-0.45	-2.75	.015
PRS-R: S, *T-* 分數									
意力不足/認知問題	77.34 ± 13.04	68.91 ± 13.58	64.99 ± 13.47	-8.43 (-13.36, -3.50)	-0.63	-6.17 (-8.68, -3.66)	-0.93	-6.17	<.001
動衝動	83.48 ± 23.90	68.98 ± 16.40	66.65 ± 16.19	-14.50 (-20.24, -8.75)	-0.71	-8.41 (-11.46, -5.36)	-0.82	-8.41	<.001
立反抗	69.45 ± 13.50	65.70 ± 12.65	64.40 ± 13.63	-3.75 (-9.22, 1.72)	-0.29	-2.53 (-4.84, -0.21)	-0.37	-2.53	.050

縮寫：CGI-ADHD-S = Clinical Global Impressions-ADHD-Severity; CPRS-R:S = Conners' Parent Rating Scales-Revised: Short Form

表 10 (Table 10)： ADHD 患者的執行功能在用藥前、用藥後 4 週、用藥後 12 週之比較

原始分數 (Z 分數)	用藥前 平均值±標準差	4 週 平均值±標準差	12 週 平均值±標準差	4 週 - 用藥前 β (95% CI)	d	12 週 - 用藥前 β (95% CI)	d
Intradimension/Extradimension Shift							
Extra-dimensional shift errors	15.5 ± 11.3 (0.74 ± 1.23)	10.2 ± 10.6 (0.16 ± 1.15)	9.3 ± 10.1 (0.07 ± 1.09)	-0.58 (-1.11, -0.05)	-0.49	-0.34 (-0.56, -0.12)	-0.58
Pre-extra-dimensional shift errors	9.8 ± 6.1 (0.70 ± 1.52)	7.1 ± 3.0 (0.03 ± 0.75)	8.9 ± 5.5 (0.47 ± 1.37)	-0.68 (-1.21, -0.15)	-0.56	-0.12 (-0.42, 0.18)	-0.16
Completed stages	7.8 ± 1.4 (-0.98 ± 1.68)	8.3 ± 0.9 (-0.36 ± 1.07)	8.4 ± 1.4 (-0.32 ± 1.69)	0.62 (-0.04, 1.28)	0.44	0.33 (-0.05, 0.71)	0.39
Total errors(adjusted)	44.6 ± 34.0 (1.02 ± 1.57)	28.3 ± 22.0 (0.26 ± 1.01)	31.1 ± 34.9 (0.39 ± 1.61)	-0.75 (-1.36, -0.14)	-0.63	-0.31 (-0.62, -0.01)	-0.59
Total trials (adjusted)	133.5 ± 58.6 (1.07 ± 1.52)	104.4 ± 38.8 (0.32 ± 1.00)	111.4 ± 63.4 (0.50 ± 1.64)	-0.75 (-1.34, -0.16)	-0.57	-0.29 (-0.59, 0.02)	-0.39
Rapid Visual Information Processing							
Total hits	10.8 ± 5.8 (-1.04 ± 1.21)	13.7 ± 5.7 (-0.45 ± 1.17)	13.6 ± 6.9 (-0.45 ± 1.43)	0.59 (0.21, 0.97)	0.50	0.29 (0.08, 0.50)	0.44
Total misses	16.2 ± 5.8 (1.03 ± 1.20)	13.3 ± 5.6 (0.44 ± 1.16)	13.4 ± 6.9 (0.45 ± 1.43)	-0.59 (-0.97, -0.22)	-0.50	-0.29 (-0.50, -0.08)	-0.44
Probability of hits	0.40 ± 0.22 (-1.05 ± 1.20)	0.51 ± 0.21 (-0.46 ± 1.16)	0.50 ± 0.26 (-0.47 ± 1.43)	0.59 (0.21, 0.97)	0.51	0.29 (0.08, 0.50)	0.42
Total correct rejections	230.4 ± 15.1 (-1.39 ± 1.33)	236.1 ± 17.7 (-0.88 ± 1.56)	239.8 ± 16.8 (-0.55 ± 1.49)	0.51 (0.18, 0.84)	0.35	0.42 (0.24, 0.59)	0.59
Total false alarms	6.9 ± 7.3 (1.15 ± 1.77)	7.3 ± 9.6 (1.25 ± 2.34)	4.2 ± 6.1 (0.49 ± 1.50)	0.10 (-0.79, 0.99)	0.05	-0.33 (-0.66, -0.00)	-0.40
Probability of false alarms	0.03 ± 0.03 (0.96 ± 1.55)	0.03 ± 0.04 (1.03 ± 2.00)	0.02 ± 0.03 (0.38 ± 1.31)	0.06 (-0.69, 0.81)	0.04	-0.29 (-0.58, -0.01)	-0.38
A'	0.82 ± 0.08	0.85 ± 0.08	0.86 ± 0.08	0.65 (0.27, 1.04)	0.38	0.43 (0.20, 0.66)	0.50

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				β	β (95% CI)	β	β (95% CI)
(continued)	(−1.44 ± 1.59)	(−0.78 ± 1.51)	(−0.58 ± 1.54)				
Mean latency (ms)	639 ± 201 (1.54 ± 1.72)	562 ± 171 (0.87 ± 1.46)	502 ± 136 (0.36 ± 1.16)	−0.80	−0.59 (−0.84, −0.33)	−0.42	−0.66 (−1.14, −0.19)
Spatial Span							
Span length	5.9 ± 1.4 (−1.14 ± 1.05)	6.4 ± 1.5 (−0.78 ± 1.09)	6.8 ± 1.4 (−0.46 ± 1.04)	0.64	0.34 (0.16, 0.52)	0.34	0.36 (−0.07, 0.79)
Total errors	13.4 ± 6.5 (0.07 ± 0.98)	13.8 ± 6.9 (0.14 ± 1.03)	13.2 ± 6.7 (0.05 ± 1.01)	−0.02	−0.01 (−0.25, 0.23)	0.07	0.07 (−0.39, 0.53)
Total usage errors	2.5 ± 1.7 (0.77 ± 1.26)	1.9 ± 1.3 (0.31 ± 0.98)	1.4 ± 1.5 (−0.05 ± 1.10)	−0.69	−0.41 (−0.65, −0.17)	−0.40	−0.46 (−0.81, −0.11)
Spatial Working Memory							
Total errors	34.1 ± 20.0 (1.05 ± 1.36)	31.9 ± 21.5 (0.91 ± 1.46)	27.5 ± 19.3 (0.61 ± 1.31)	−0.33	−0.22 (−0.42, −0.03)	−0.10	−0.15 (−0.61, 0.32)
Strategy utilization	34.5 ± 6.6 (0.48 ± 1.38)	32.7 ± 5.9 (0.11 ± 1.24)	31.7 ± 5.4 (−0.11 ± 1.12)	−0.47	−0.30 (−0.48, −0.11)	−0.29	−0.38 (−0.83, 0.08)
Stocking of Cambridge							
Problems solved in minimum moves	7.6 ± 2.0 (−0.54 ± 1.01)	7.7 ± 2.2 (−0.51 ± 1.11)	8.8 ± 1.8 (0.07 ± 0.91)	0.64	0.31 (0.10, 0.51)	0.03	0.03 (−0.47, 0.54)
Mean moves	18.2 ± 2.1 (0.56 ± 0.97)	17.6 ± 2.2 (0.26 ± 1.00)	17.0 ± 2.0 (−0.01 ± 0.91)	−0.60	−0.28 (−0.50, −0.06)	−0.30	−0.29 (−0.78, 0.19)
Mean initial thinking time (ms)	3981 ± 2894 (−0.32 ± 1.03)	3128 ± 1981 (−0.62 ± 0.71)	3069 ± 2309 (−0.65 ± 0.82)	−0.35	−0.16 (−0.31, −0.01)	−0.34	−0.30 (−0.63, 0.03)
Mean subsequent thinking time (ms)	1682 ± 1510 (0.77 ± 1.31)	753 ± 945 (−0.04 ± 0.82)	452 ± 370 (−0.30 ± 0.32)	−1.12	−0.53 (−0.77, −0.30)	−0.74	−0.81 (−1.32, −0.29)

縮寫：β = z 分數差異 的 估計值

表 11 (Table 11)： ADHD 患者的視覺記憶在用藥前、用藥後 4 週、用藥後 12 週之比較

原始分數 (z 分數)	用藥前 平均值±標準差	4 週 平均值±標準差	12 週 平均值±標準差	4 週 - 用藥前 β (95% CI)	d	12 週 - 用藥前 β (95% CI)	d
Pattern Recognition Memory							
Mean latency of correct responses(ms)	1874.5 ± 606.5	1625.6 ± 367.7	1597.2 ± 497.7	-0.52 (-0.84, -0.19)	-0.50[b]	-0.29 (-0.42, -0.15)	-0.50[c]
	(0.10 ± 1.26)	(-0.41 ± 0.76)	(-0.47 ± 1.03)				
Total correct responses	21.53 ± 2.19	22.47 ± 1.20	21.97 ± 1.69	0.47 (0.07, 0.88)	0.53[a]	0.11 (-0.08, 0.30)	0.22
	(-0.29 ± 1.11)	(0.19 ± 0.61)	(-0.07 ± 0.86)				
Spatial Recognition Memory							
Mean latency of correct responses(ms)	1932.1 ± 743.9	1799.0 ± 603.5	1647.9 ± 588.2	-0.22 (-0.64, 0.20)	-0.20	-0.23 (-0.44, -0.03)	-0.42[a]
	(0.05 ± 1.22)	(-0.17 ± 0.99)	(-0.42 ± 0.97)				
Total correct responses	15.90 ± 2.14	16.03 ± 2.33	15.77 ± 2.30	0.09 (-0.40, 0.57)	0.06	-0.04 (-0.26, 0.17)	-0.06
	(-0.94 ± 1.37)	(-0.86 ± 1.49)	(-1.03 ± 1.47)				

[a] $p < .05$.
[b] $p < .01$.
[c] $p < .001$.

縮寫：β＝z 分數差異的估計值

表 12 (Table 12)： ADHD 患者和對照組的人口學特質與智商

平均值±標準差	ADHD (n=25)	對照組 (n=25)	*F*	*p*
男/女	22/3	22/3		
年齡 (範圍:8-17)	11.4±2.1	11.4±2.7	0.04	.840
全智商	108.4±12.7	111.1±10.9	1.66	.209
操作智商	105.9±15.4	107.0±12.4	0.13	.718
語言智商	109.8±10.9	113.1±10.9	2.57	.122
Verbal Comprehension Index	110.9±10.0	113.5±10.9	1.82	.191
Perceptual Organization Index	107.3±14.6	108.0±12.8	0.07	.796
Freedom from Distractibility Index	105.3±15.9	110.8±11.7	2.26	.146
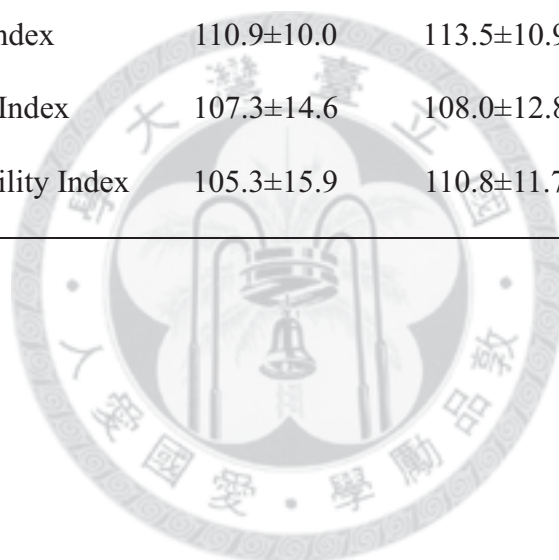
表 13 (Table 13)： ADHD 患者和對照組的執行功能比較

平均值±標準差	ADHD	對照組	F	p	Cohen's d
Intra-Extra Dimensional Set Shift					
Total errors (adjusted)	38.48±22.12	23.84±19.04	6.29	.019	0.71
Total trials (adjusted)	125.04±38.72	94.28±34.21	8.86	.007	0.84
Rapid Visual Information Processing					
Probability of hits	0.38±0.18	0.51±0.17	9.46	.005	-0.73
Probability of false alarm	0.03±0.03	0.01±0.02	5.85	.024	0.68
B''	0.74±0.20	0.89±0.12	12.55	.002	-0.92
Mean latency (ms)	626.00±195.60	490.94±144.87	8.60	.007	0.78
Spatial Working Memory					
Strategy utilization	35.44±5.05	31.88±4.93	6.36	.019	0.71
Total errors	36.32±17.69	24.68±19.22	4.97	.036	0.63
Stockings of Cambridge					
Problems solved in minimum moves	7.08±1.63	7.88±1.86	4.00	.057	-0.46
Total moves	19.29±2.63	17.50±1.55	9.07	.006	0.83
Mean initial thinking time(ms)	3289.11±1751.51	4713.62±2240.03	7.05	.014	-0.71
Mean subsequent thinking time(ms)	1806.92±1936.87	1079.71±601.43	3.97	.058	0.51

表 14 (Table 14)： 額葉紋狀體神經路徑預測 ADHD 患者的注意力不足與過動衝動症狀

| | | SNAP-IV | | | |
| | | 注意力不足 | | 過動衝動 | |
		β	p	β	p
背外側前額葉	L	-	-	-394.25	.001
內側前額葉	R	-	-	-279.11	.006
眼窩額葉	R	-127.09	<.001	-	-
腹外側前額葉	R	-	-	-131.77	.068
F values		$F_{(1,22)} = 16.54, p < .001$		$F_{(3,20)} = 6.96, p = .002$	
R-square		0.43		0.51	

縮寫：L, 左側; R, 右側; SNAP-IV, the Chinese version of the Swanson, Nolan, and Pelham, version IV scale.

表 15 (Table 15)：額葉紋狀體神經路徑預測 ADHD 患者與對照組的執行功能測驗表現

		Intra-Extra Dimensional Set Shift				Rapid Visual Information Processing					
		Total errors (adjusted)		Total trials (adjusted)		Probability of false alarm		B"		Mean latency (ms)	
		β	p	β	p	β	p	β	p	β	p
ADHD											
眼窩額葉	L	456.94	.007	757.54	.010	0.68	.012	-4.22	.014	-	-
	R	-	-	-	-	-	-	-	-	-	-
腹外側前額葉	L	-442.06	.002	-774.31	.002	-	-	-2.84	.082	-	-
	R	-	-	-	-	-	-	5.76	.015	-	-
F values		$F_{(2,22)} = 8.13, p = .002$		$F_{(2,22)} = 7.63, p = .003$		$F_{(1,23)} = 7.39, p = .012$		$F_{(3,21)} = 3.88, p = .024$		-	
R-square		0.42		0.41		0.24		0.36		-	
對照組											
內側前額葉	L	-	-	-	-	-0.19	.084	1.24	.082	-	-
眼窩額葉	L	262.66	.022	419.36	.042	-	-	-	-	3936.40	<.001
	R	-	-	-	-	-	-	-	-	-	-
腹外側前額葉	R	-430.10	.003	-761.64	.004	-	-	-	-	-2946.83	.009
F values		$F_{(2,22)} = 5.96, p = .009$		$F_{(2,22)} = 5.43, p = .012$		$F_{(1,23)} = 3.26, p = .084$		$F_{(1,23)} = 3.32, p = .082$		$F_{(2,22)} = 8.75, p = .002$	
R-square		0.35		0.33		0.12		0.13		0.44	

Continued

		Spatial Working Memory				**Stockings of Cambridge**							
		Strategy utilization		Total errors		Problems solved in minimum moves		Total moves		Mean initial thinking time		Mean subsequent thinking time	
		β	p	β	p	β	p	β	p	β	p	β	p
ADHD													
背外側前額葉	L	-	-	-	-	-	-	-	-	-	-	61874.84	.014
眼窩額葉	L	78.37	.054	334.50	.016	-	-	-	-	-34690.97	.013	-	-
	R	-	-	-	-	-34.30	.006	40.33	.063	-	-	-	-
腹外側前額葉	L	-	-	-	-	-	-	-	-	-	-	-32675.44	.061
F values		F$_{(1,23)}$ =4.13, p=.054		F$_{(1,23)}$ =6.72, p =.016		F$_{(1,23)}$ =9.12, p =.006		F$_{(1,23)}$ =3.85, p=.063		F$_{(1,23)}$ =7.40, p =.013		F$_{(2,21)}$ =3.60, p =.045	
R-square		0.15		0.23		0.28		0.15		0.25		0.26	
對照組													
背外側前額葉	R	-230.16	.010	-590.66	.003	-	-	-29.09	.016	40362.23	.022	-	-
內側前額葉	R	184.25	.048	-	-	-	-	-	-	-	-	-	-
眼窩額葉	L	-	-	300.41	.014	-	-	-	-	-	-	-	-
腹外側前額葉	L	-	-	-285.43	.025	-	-	-	-	-	-	-	-
	R	-	-	326.56	.043	-	-	-	-	-	-	-	-
F values		F$_{(2,22)}$ =3.11, p =.048		F$_{(4,20)}$=4.39, p =.010				F$_{(1,23)}$=6.75, p =.016		F$_{(1,23)}$=6.04, p =.022		-	
R-square		0.31		0.47				0.23		0.21			

縮寫：L，左側；R，右側

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表 16 (Table 16)： DAT1 基因上 15 個標記的位置與次要對偶基因頻率 (minor allele frequency, MAF)

基因標記	基因位置	染色體位置	對偶基因	MAF (%)
rs2937639	Intron 1	1496728	A/G	14.6
rs2617605	Intron 2	1495521	A/G	17.3
rs403636	Intron 2	1491354	G/T	32.0
rs463379	Intron 4	1484164	G/C	47.5
rs393795	Intron 4	1481514	A/C	47.3
rs37020	Intron 6	1471374	G/T	33.7
rs40358	Intron 7	1469142	T/G	35.0
rs37022	Intron 7	1468629	A/T	50.0
rs466630	Inton 7	1468404	G/C	49.3
rs27048	Intron 8	1465645	C/T	17.9
rs429699	Intron 11	1462127	C/T	25.1
rs40184	Intron 14	1448077	G/A	26.1
rs1042098	3´UTR	1447815	T/C	10.6
rs27072	3´UTR	1447522	C/T	26.9
3´VNTR	3´UTR	1446863	9/10 repeats	5.9

表 16 (Table 16)： DAT1 基因上 15 個標記的位置與次要對偶基因頻率 (minor allele frequency, MAF)
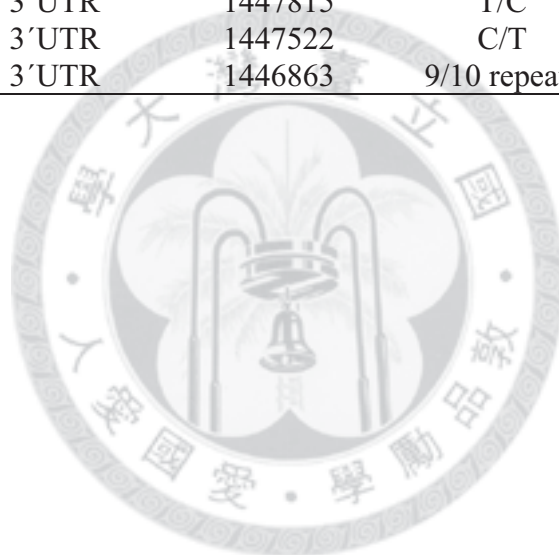
表 17 (Table 17)： DAT1 基因上 15 個標記與注意力不足亞型之關聯性

基因標記	對偶基因	對偶基因頻率	Informative 家庭總數	Z	p
rs2937639	G	0.146	38	0.438	0.662
rs2617605	G	0.173	46	0.384	0.701
rs403636	T	0.32	50	0.232	0.816
rs463379	C	0.475	46	0.563	0.574
rs393795	C	0.473	46	0.563	0.574
rs37020	T	0.337	47	0.232	0.816
rs40358	T	0.65	54	0.471	0.637
rs37022	T	0.5	49	0.229	0.819
rs466630	C	0.493	39	0.679	0.497
rs27048	C	0.821	35	1.511	0.131
rs429699	T	0.251	44	2.393	0.017*
rs40184	G	0.739	48	1.746	0.081
rs1042098	T	0.894	29	0.557	0.577
rs27072	C	0.731	42	0.361	0.718
3´VNTR	10	0.916	20	1.877	0.061

* <0.05
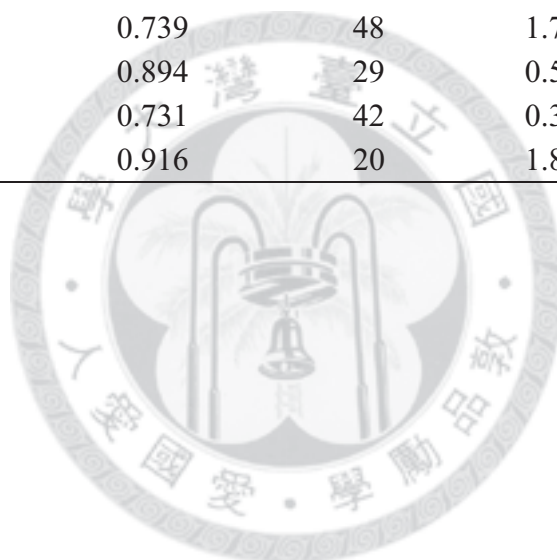
表 18 (Table 18)：DAT1 基因上 3 個單套體區間與 ADHD 不同亞型之關聯性

單套體區間	單套體頻率	Informative 家庭總數			Z			P			P_2 side by haplotype permutation test			Minimal P		
		T	C	IA	T	C	IA	T	C	IA	T	C	IA	T	C	IA
rs403636, rs463379, rs393795, and rs37020																
G/G/A/G	0.513	141	102	53	0	0.583	-0.454	1	0.560	0.650	0.985	0.578	0.668			
T/C/C/T	0.311	136	94	53	-0.571	-1.209	0.355	0.568	0.226	0.723	0.591	0.224	0.704			
G/C/C/G	0.136	89	59	40	1.512	2.069	0.415	0.130	0.039*	0.678	0.123	0.036*	0.601			
G/C/C/T	0.021	15	7	8	-0.763	NC	NC	0.445	NC	NC	0.442	NC	NC	0.546	0.127	0.987
rs27048 and rs429699																
C/C	0.578	171	111	68	-1.542	-1.578	-1.251	0.123	0.115	0.211	0.116	0.093	0.223			
C/T	0.245	127	84	50	2.004	1.142	2.633	0.045*	0.254	0.008*	0.034*	0.258	0.006*			
T/C	0.177	111	79	39	-0.392	0.615	-1.432	0.695	0.539	0.152	0.697	0.556	0.175	0.100	0.257	0.022*
rs1042098, rs27072, and 3' VNTR																
T/C/10	0.621	142	99	57	0.591	-0.774	1.235	0.554	0.439	0.217	0.524	0.434	0.194			
T/T/10	0.275	123	85	49	0.502	1.219	-0.365	0.616	0.223	0.715	0.669	0.245	0.638			
C/C/9	0.064	44	28	16	-1.633	-0.354	-1.886	0.102	0.724	0.059	0.085	0.662	0.033*	0.341	0.866	0.228

縮寫：NC = informative 家庭總數小於 10; T: 所有樣本; C: 混合亞型; IA: 注意力不足亞型
* <0.05

表 19 (Table 19)： DAT1 基因上 15 個標記與 ADHD 之關聯性

基因標記	對偶基因	對偶基因頻率	Informative 家庭總數	Z	p
rs2937639	G	0.144	115	0.758	0.448
rs2617605	G	0.172	134	1.018	0.309
rs403636	G	0.697	167	1.694	0.090
rs463379	C	0.464	182	0.368	0.713
rs393795	C	0.462	178	0.370	0.711
rs37020	G	0.675	165	1.619	0.106
rs40358	T	0.657	179	1.836	0.066
rs37022	T	0.502	189	0.300	0.764
rs466630	C	0.489	152	0.058	0.953
rs27048	T	0.175	142	1.018	0.309
rs429699	C	0.756	158	1.742	0.081
rs40184	G	0.731	167	0.195	0.845
rs1042098	T	0.897	99	0.396	0.691
rs27072	T	0.272	150	0.142	0.887
3´VNTR	10	0.918	81	1.062	0.288
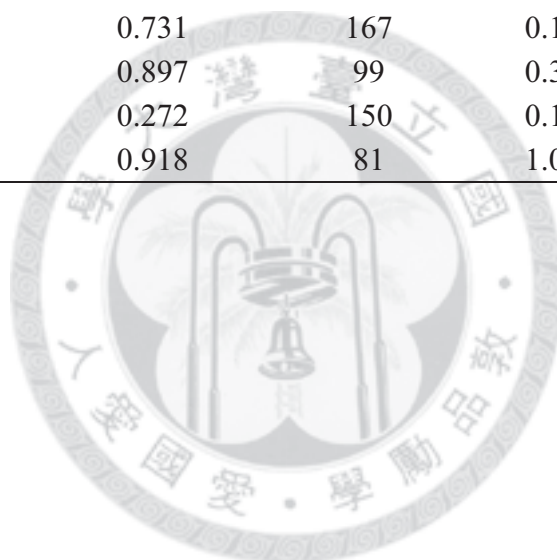
表 20 (Table 20)：DAT1 基因上 15 個標記與空間工作記憶之關聯性

基因標記	對偶基因	對偶基因頻率	Informative 家庭總數				Z				P			
			w-e	w-e (8)	d-e	d-e (8)	w-e	w-e (8)	d-e	d-e (8)	w-e	w-e (8)	d-e	d-e (8)
rs2937639	G	0.144	68	51	49	39	1.968	1.866	1.94	1.741	0.049[a]	0.062	0.052	0.082
rs2617605	G	0.172	76	58	55	45	2.847	2.702	3.053	2.61	0.004[b]	0.007[b]	0.002[b]	0.009[b]
rs403636	G	0.697	104	80	84	64	1.106	1.292	2.258	1.637	0.269	0.196	0.024[a]	0.102
rs463379	C	0.464	103	87	88	74	1.577	1.306	0.761	0.8	0.115	0.191	0.447	0.424
rs393795	C	0.462	101	85	86	72	1.702	1.475	0.847	0.907	0.089	0.140	0.396	0.364
rs37020	G	0.675	106	83	86	67	1.708	1.608	2.858	2.126	0.087	0.108	0.004[b]	0.033[a]
rs40358	T	0.657	109	88	90	69	0.669	0.902	1.242	0.911	0.504	0.367	0.214	0.362
rs37022	T	0.502	100	82	85	69	0.985	0.671	0.438	0.336	0.325	0.502	0.661	0.737
rs466630	C	0.489	81	65	63	51	0.631	0.181	0.159	0.273	0.528	0.856	0.874	0.785
rs27048	T	0.175	78	64	64	53	0.649	0.357	0.768	0.583	0.516	0.721	0.442	0.560
rs429699	C	0.756	83	67	71	58	0.873	1.057	1.325	1.494	0.383	0.290	0.185	0.135
rs40184	G	0.731	91	73	75	59	1.233	1.185	1.015	1.054	0.218	0.236	0.310	0.292
rs1042098	T	0.897	65	54	52	40	0.377	0.381	0	0.175	0.706	0.703	1	0.861
rs27072	T	0.272	79	61	59	51	0.51	0.108	0.606	0.305	0.610	0.914	0.545	0.760
3'UTR	10	0.918	48	38	35	27	1.684	1.111	1.042	0.869	0.092	0.267	0.298	0.385

縮寫：w-e, within-search errors; w-e (8), within-search errors 8 boxes; d-e, double errors; d-e, double errors 8 boxes.
[a] $P < 0.05$.
[b] $P < 0.01$.

表 21 (Table 21)：DAT1 基因上 3 個單套體區間與空間工作記憶之關聯性

單套體	單套體頻率	Informative 家庭總數				Z				P				$P_{2\,side}$ by haplotype permutation test				Minimal P			
		w-e	w-e (8)	d-e	d-e (8)	w-e	w-e (8)	d-e	d-e (8)	w-e	w-e (8)	d-e	d-e (8)	w-e	w-e (8)	d-e	d-e (8)	w-e	w-e (8)	d-e	d-e (8)
rs403636, rs463379, rs393795, and rs37020																					
G/G/A/G	0.521	108	90	90	75	-1.435	-1.201	-0.784	-0.861	0.151	0.230	0.433	0.389	0.155	0.230	0.433	0.390				
T/C/C/T	0.3	112	89	91	73	-0.834	-0.754	-1.869	-1.296	0.404	0.451	0.062	0.195	0.408	0.453	0.060	0.195				
G/C/C/G	0.137	74	54	54	41	3.471	3.219	3.382	3.044	0.0005[c]	0.001[b]	0.0007[c]	0.002[b]	0.0003[c]	0.0003[c]	0.0004[c]	0.0007[c]	0.001[b]	0.002[b]	0.001[b]	0.004[b]
G/C/C/T	0.023	15	12	12	10	-1.252	-1.372	-1.265	-1.306	0.211	0.170	0.206	0.192	0.235	0.181	0.218	0.207				
rs27048 and rs429699																					
C/C	0.58	123	101	100	83	0.149	0.577	0.383	0.682	0.882	0.564	0.702	0.496	0.941	0.536	0.711	0.531				
C/T	0.244	91	75	76	62	-0.868	-1.046	-1.235	-1.409	0.385	0.296	0.217	0.159	0.394	0.265	0.201	0.178				
T/C	0.176	80	67	68	56	0.753	0.406	0.866	0.664	0.451	0.685	0.387	0.507	0.459	0.751	0.409	0.490	0.639	0.541	0.457	0.353
rs27072, and 3'UTR																					
C/10	0.643	101	76	77	61	0.095	0.488	-0.328	0.074	0.924	0.625	0.743	0.941	0.905	0.611	0.760	0.921				
T/10	0.273	84	63	64	51	1.135	0.095	1.042	0.438	0.256	0.925	0.297	0.662	0.276	0.981	0.349	0.693				
C/9	0.061	36	31	30	23	-0.509	-0.529	-0.386	-0.435	0.611	0.597	0.700	0.663	0.630	0.604	0.738	0.658	0.575	0.945	0.919	0.942

縮寫：w-e, within-search errors; w-e (8), within-search errors 8 boxes; d-e, double errors; d-e (8), double errors 8 boxes.

[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.

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圖 1 (Figure 1)： ADHD 患者、未發病手足、與對照組在 a) Spatial Working Memory 測驗中 4-box, 6-box, 和 8-box 問題的總錯誤數; b) Stocking of Cambridge 測驗中平均移動次數
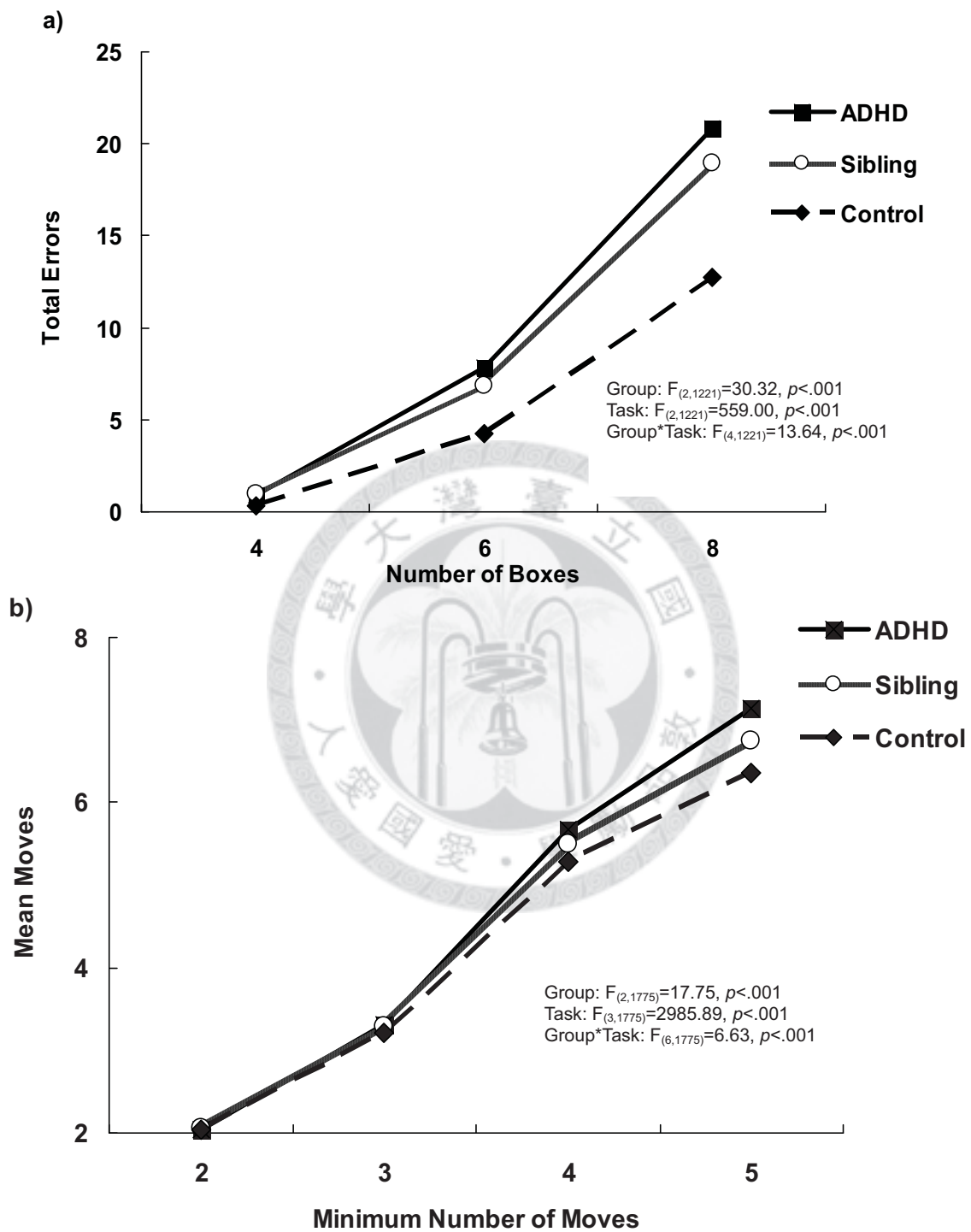

a)

Group: $F_{(2,1221)}=30.32$, $p<.001$
Task: $F_{(2,1221)}=559.00$, $p<.001$
Group*Task: $F_{(4,1221)}=13.64$, $p<.001$

b)

Group: $F_{(2,1775)}=17.75$, $p<.001$
Task: $F_{(3,1775)}=2985.89$, $p<.001$
Group*Task: $F_{(6,1775)}=6.63$, $p<.001$

圖 2 (Figure 2)： ADHD 患者、未發病手足、與對照組在 Delayed Matching to Sample 測驗中 simultaneous, short delay, medium delay,與 long delay 的正確反應百分比

Delayed Matching to Sample
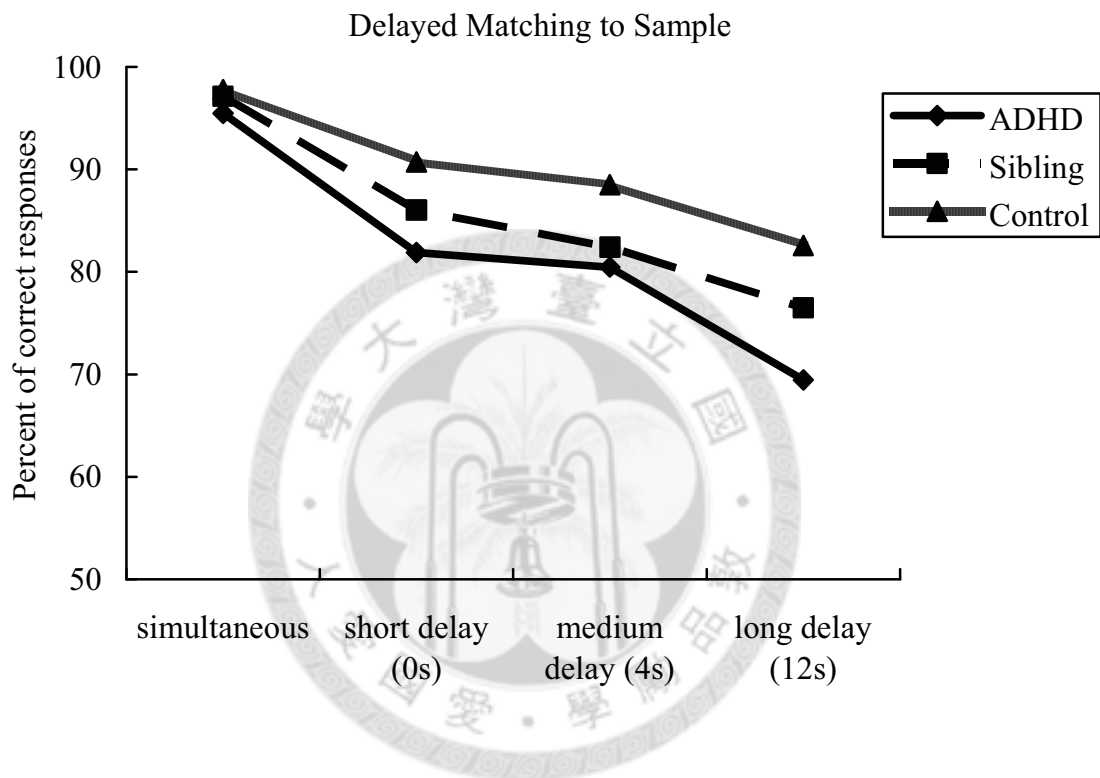
圖 3 (Figure 3)： ADHD 患者的視覺記憶在用藥前、用藥後 4 週、用藥後 12 週之比較. *p <.05; ** p <.01; *** p <.001.

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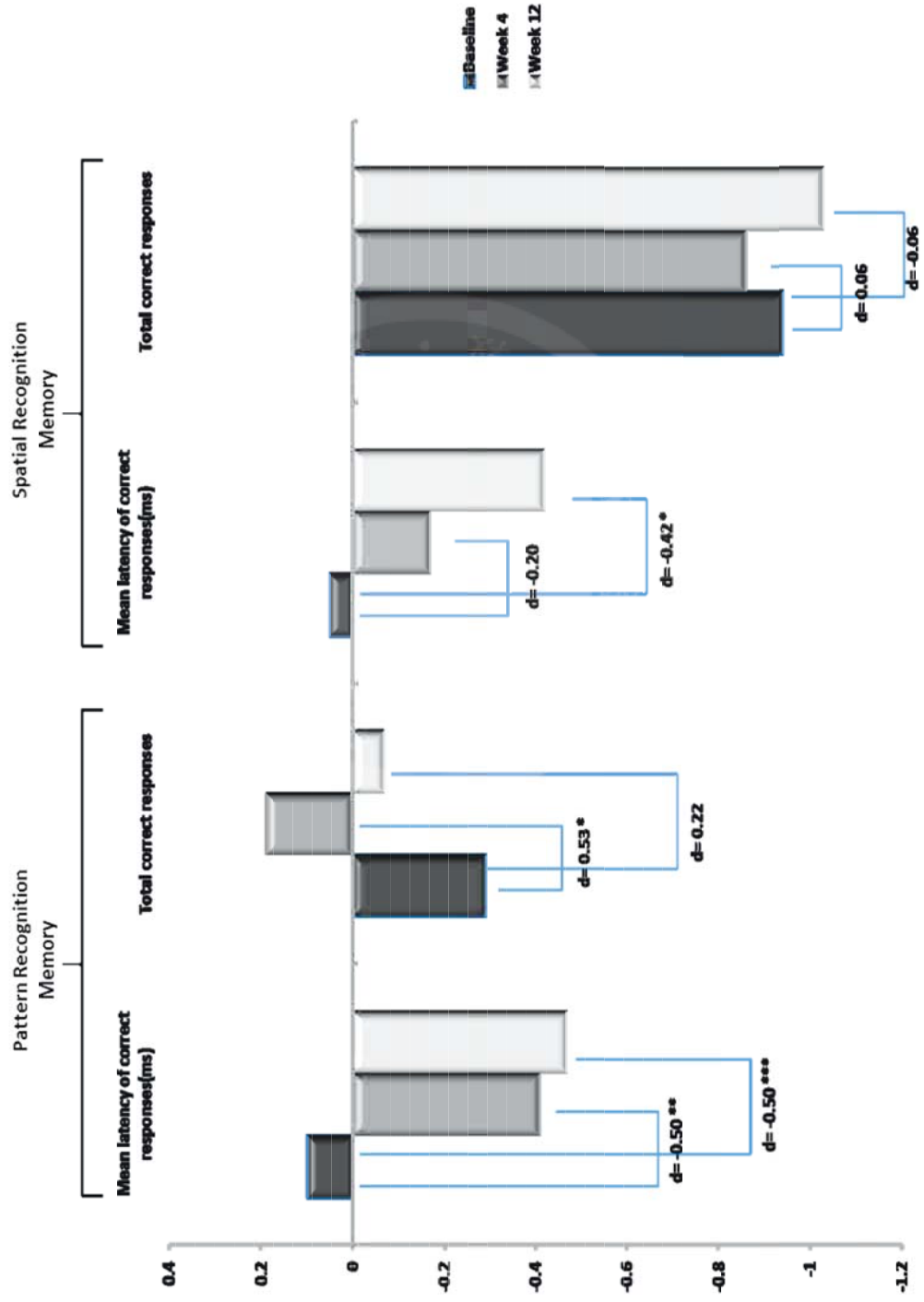
圖 4 (Figure 4)： Regions of interest (ROIs)和額葉紋狀體神經路徑。淡黃色為 dorsolateral prefrontal cortex，淡藍色為 medial prefrontal cortex，粉紅色為 orbitofrontal cortex，棕色為 ventrolateral prefrontal cortex，赭色為 caudate nucleus。黃色為 dorsolateral prefrontal - caudate tract，藍色為 medial prefrontal – caudate tract，粉紅色為 orbitofrontal – caudate tract，橘色為 ventrolateral prefrontal – caudate tract
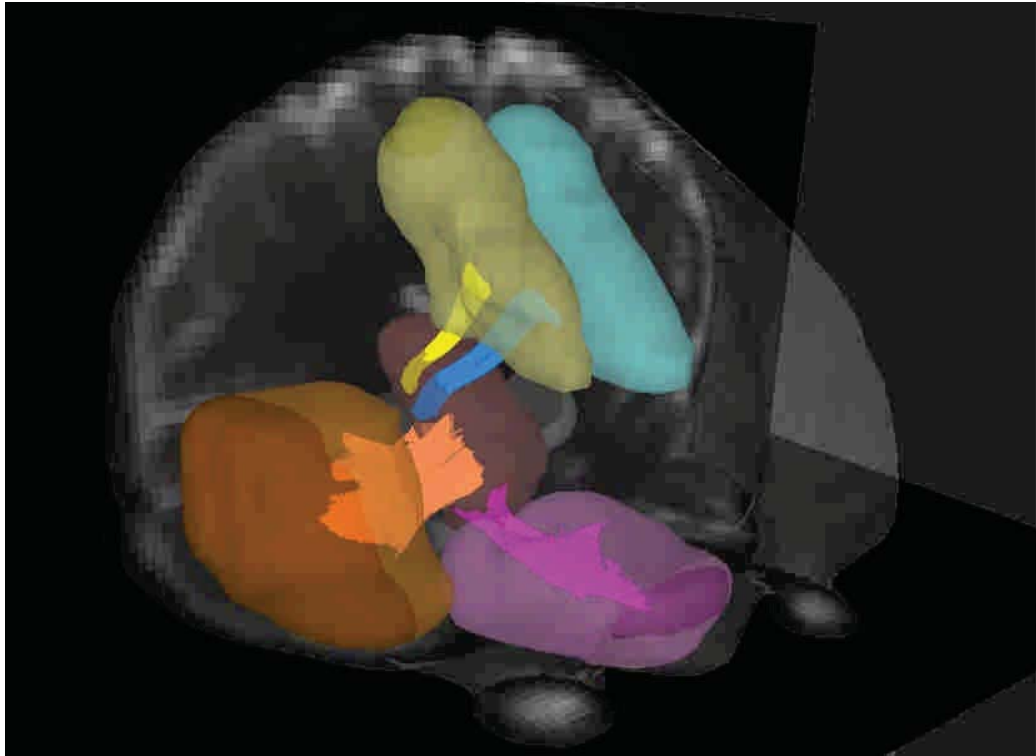
圖 5 (Figure 5)： ADHD 患者與對照組在左右兩側額葉紋狀體之 generalized fractional anisotropy 的比較; d, Cohen's *d*.
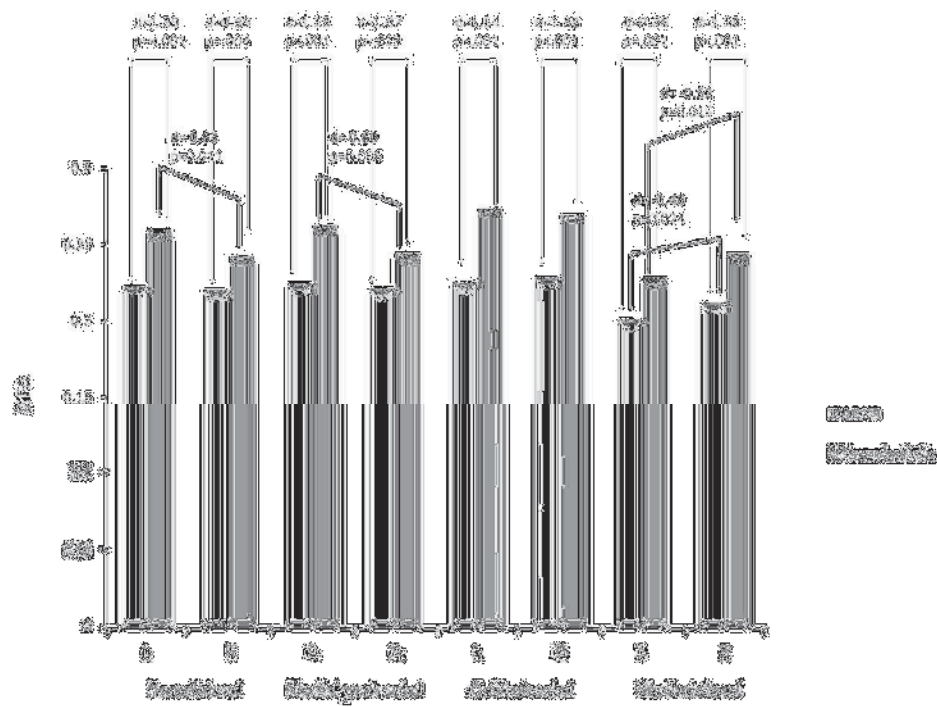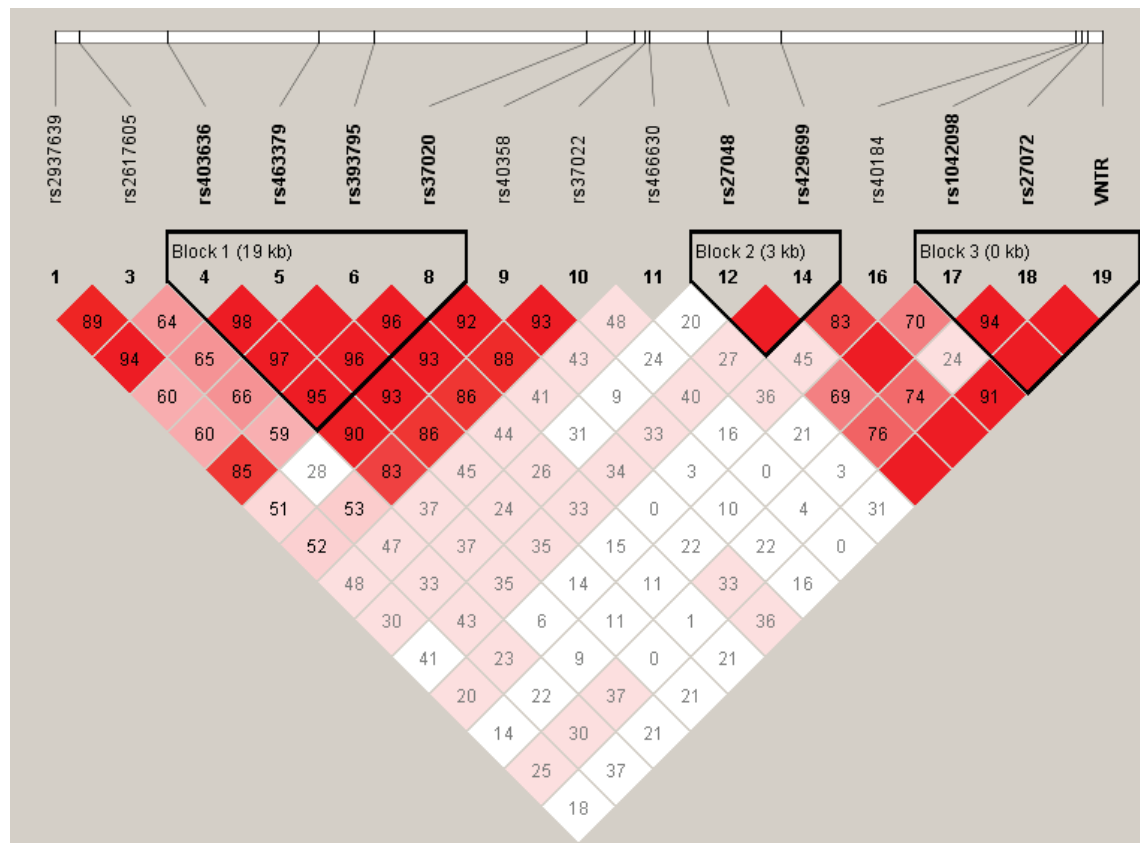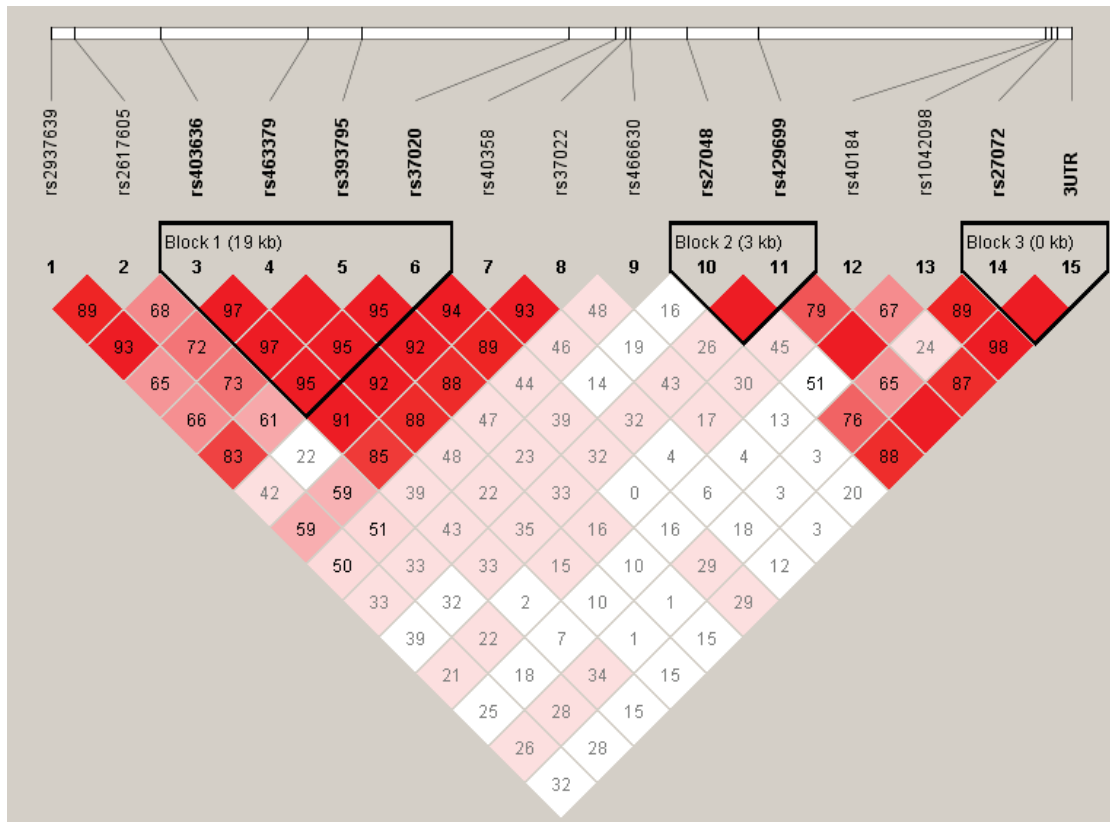
圖 6 (Figure 6)： 遺傳基因研究中，DAT1 基因的 15 個標記之連鎖不平衡

圖 7 (Figure 7)：遺傳基因與執行功能關聯性研究中，DAT1 基因的 15 個標記之連鎖不平衡

9. 附錄 (Appendix)

9.1 修業期間發表之主要論文

1. Gau SS*, Chiu CD, **Shang CY**, Cheng AT, Soong WT(2009). Executive functions at adolescence among children with attention-deficit/hyperactivity disorder. *Journal of Developmental and Behavioral Pediatrics* 30(6): 525-34.

2. Gau SS*, **Shang CY** (2010). Executive functions as endophenotypes in ADHD: Evidence from the Cambridge Neuropsychological Test Battery (CANTAB). *Journal of Child Psychology and Psychiatry* 51(7):838-49.

3. **Shang CY**, Gau SS* (2011). Visual Memory as potential cognitive endophenotypes of attention-deficit hyperactivity disorders. *Psychological Medicine* 41:2603-14.

4. Gau SS*, **Shang CY** (2010). Improvement of executive functions in boys with attention-deficit hyperactivity disorder: an open-label follow-up study with once-daily atomoxetine. *International Journal of Neuropsychopharmacology* 13(2): 243-56.

5. **Shang CY,** Gau SS* (2012). Improving visual memory, attention and school function with atomoxetine in boys with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology* 22(5):353-363.

6. **Shang CY**, Wu YH, Gau SS*, Tseng YW (2012). Disturbed microstructural integrity of the frontostriatal fiber pathways and executive dysfunction in children with attention deficit hyperactivity disorder. *Psychological Medicine.* Aug 15:1-15. [Epub ahead of print]

7. **Shang CY**, Gau SS,* Liu CM, Hwu HG (2011). Association between the dopamine transporter gene and the inattentive subtype of attention deficit hyperactivity disorder in Taiwan. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 35:421-8.

9.2 修業期間發表之其他相關論文

1. Gau SS*, **Shang CY**, Liu SK, Lin CH, Swanson JM, Liu YC, Tu CL (2008).

Psychometric properties of the Chinese version of the Swanson, Nolan, and Pelham, version IV scale- parent form. *International Journal of Methods in Psychiatric Research* 17(1):35-44.

2. Gau SS*, Lin CH, Hu FC, **Shang CY**, Swanson JM, Liu YC,   Liu SK (2009). Psychometric properties of the Chinese version of the Swanson, Nolan, and Pelham, version IV scale- Teacher Form. *Journal of Pediatric Psychology* 34(8): 850-61.

3. Gau SS*, Ni HC, **Shang CY**, Soong WT, WuYY, Lin LY, Chiu YN (2010). Psychiatric comorbidities among children and adolescents with persistent and remitted attention-deficit/hyperactivity disorder. *Australian New Zealand Journal of Psychiatry* 44(2): 135-43.

4. Gau SS, Lin YJ, **Shang CY**, Liu SK, Chiu YN (2010). Emotional/behavioral problems and functional impairment in clinic- and community-based children with attention-deficit/hyperactivity disorder in Taiwan. *Journal of Abnormal Child Psychology* 44(2):135-43.

5. Chiang HL, Gau SS*, Ni HC, Chiu YN, **Shang CY**, Wu YY, Lin LY, Tai YM, Soong WT (2010). Association between symptoms and subtypes of attention-deficit hyperactivity disorder and sleep problems/disorders. *Journal of Sleep Research* 19(4): 535-45.

6. **Shang CY**, Gau SS* (2010). Attention Deficit Hyperactivity Disorder (review) *Journal of the Formosan Medical Association* 14 (4) 395-400.

7. Yang LK, **Shang CY**, Gau SS* (2011) Psychiatric comorbidities in adolescents with attention-deficit/hyperactivity disorder and their siblings. *Canadian Journal of Psychiatry* 56:281-92.