巴金森氏症的最新進展與治療

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什麼是巴金森氏症？

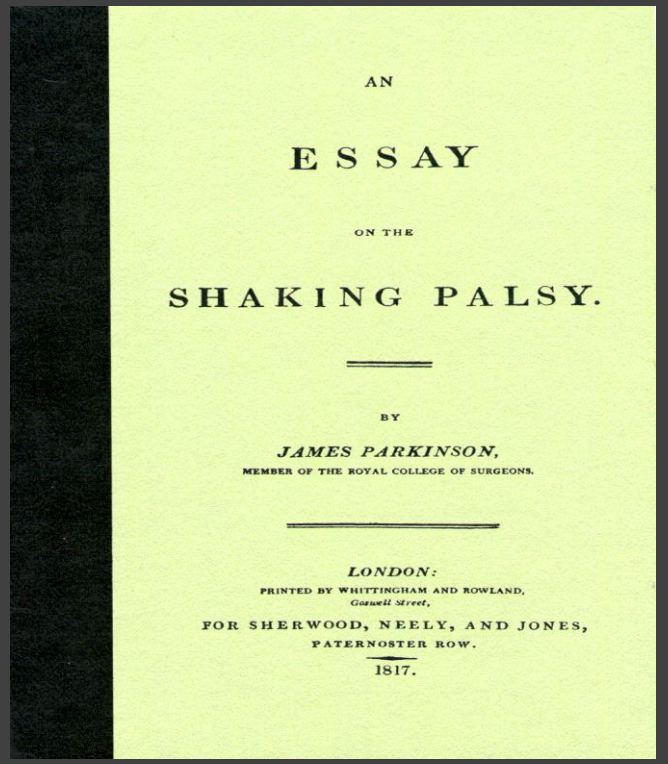
巴金森氏症(巴病)是除了阿茲海默症之外最普遍的神經退化性疾病，是一種進行性的動作障礙疾患。

發生率約佔65歲以上老年人口的1-2%，根據統計，台灣大約30000個人罹患此症(Chen et al, 2001)，發生率有隨著年齡增加而提高的現象。

少數病人的發病年齡會提早到50歲之前發病，這類病人稱之為年輕型的巴病患者，約佔所有巴病患者的4-12% (Schrag et al, 1998) 。

傑姆士.巴金森醫師
於 1817年首次發現並報告此一疾病

Dr. James Parkinson

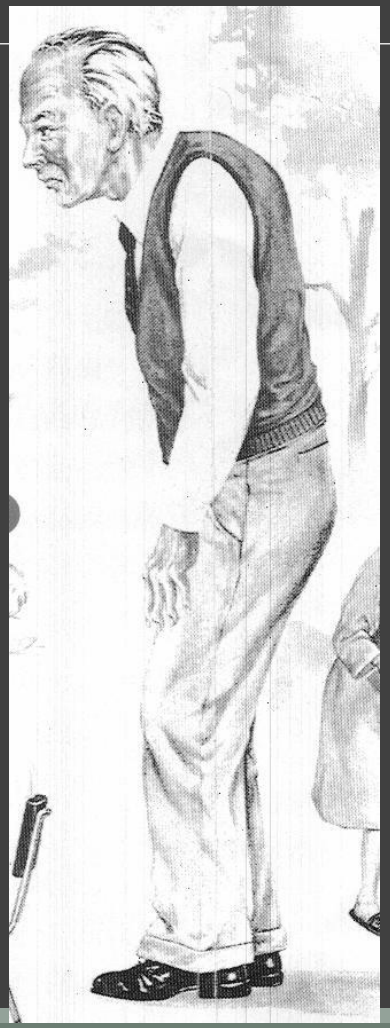


四肢發抖、無力、
軀幹駝背、動作緩慢

巴金森氏症的臨床表現

主要表現

- ✓顫抖
- ✓僵硬
- ✓動作遲緩
- ✓姿態不穩、缺乏平衡反應
- ✓書寫字體越寫越小
- ✓缺乏臉部表情(撲克臉)
- ✓講話聲調平板且小聲



巴金森病的進程

侯氏葉氏分期

第一期: 單側症狀

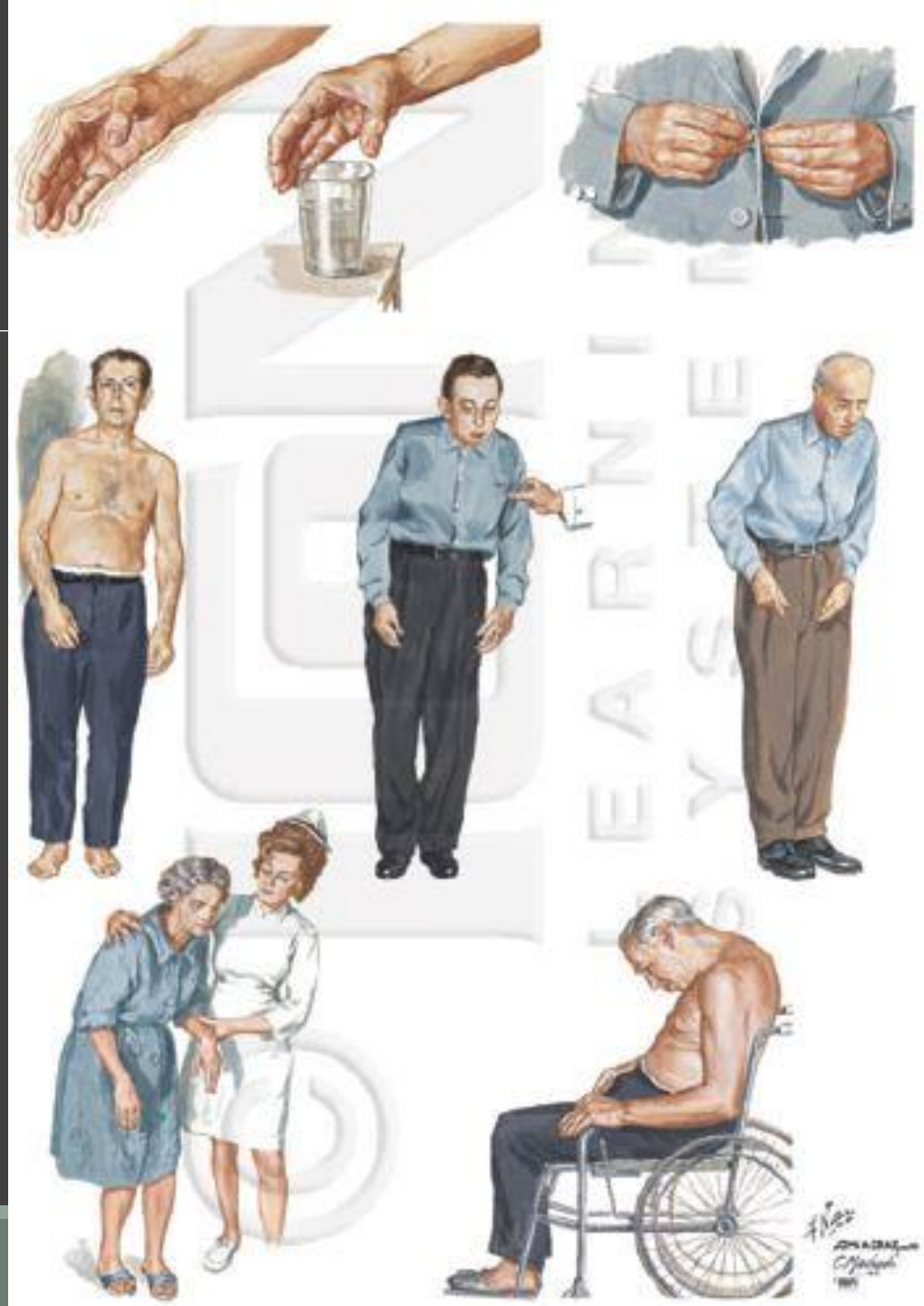
第二期: 雙側症狀

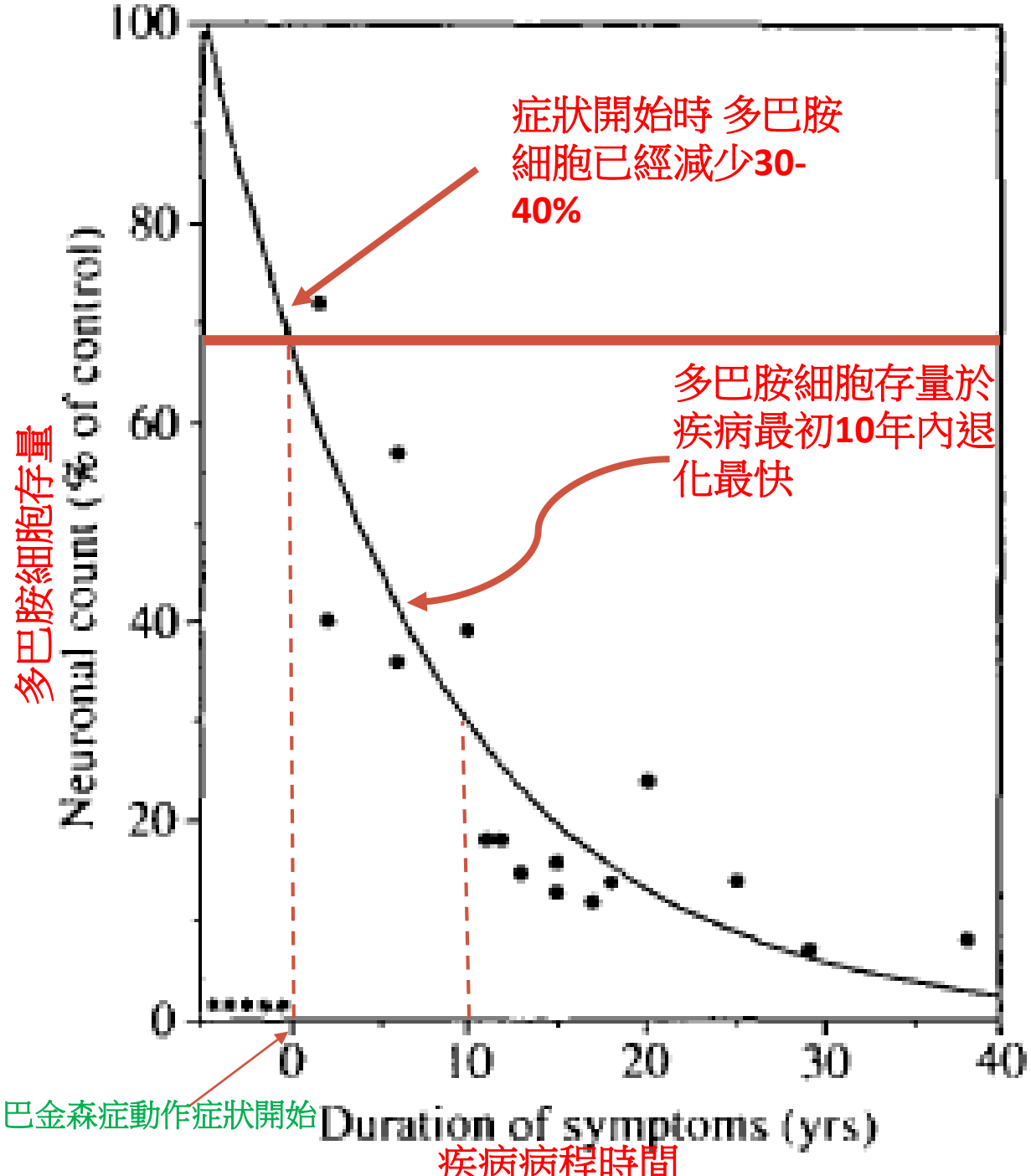
第三期: 平衡能力下降

第四期: 日常生活需人幫忙
但是還能自行走路

第五期: 仰賴輪椅

每個人的疾病進展都不相同!!!!




100
80
60
40
20
0
0
10
20
30
40
Neuronal count (% of control)
Duration of symptoms (yrs)
症狀開始時 多巴胺細胞已經減少30-40%
多巴胺細胞存量於疾病最初10年內退化最快
多巴胺細胞存量
巴金森症動作症狀開始
疾病病程時間

巴金森氏症的病理成因

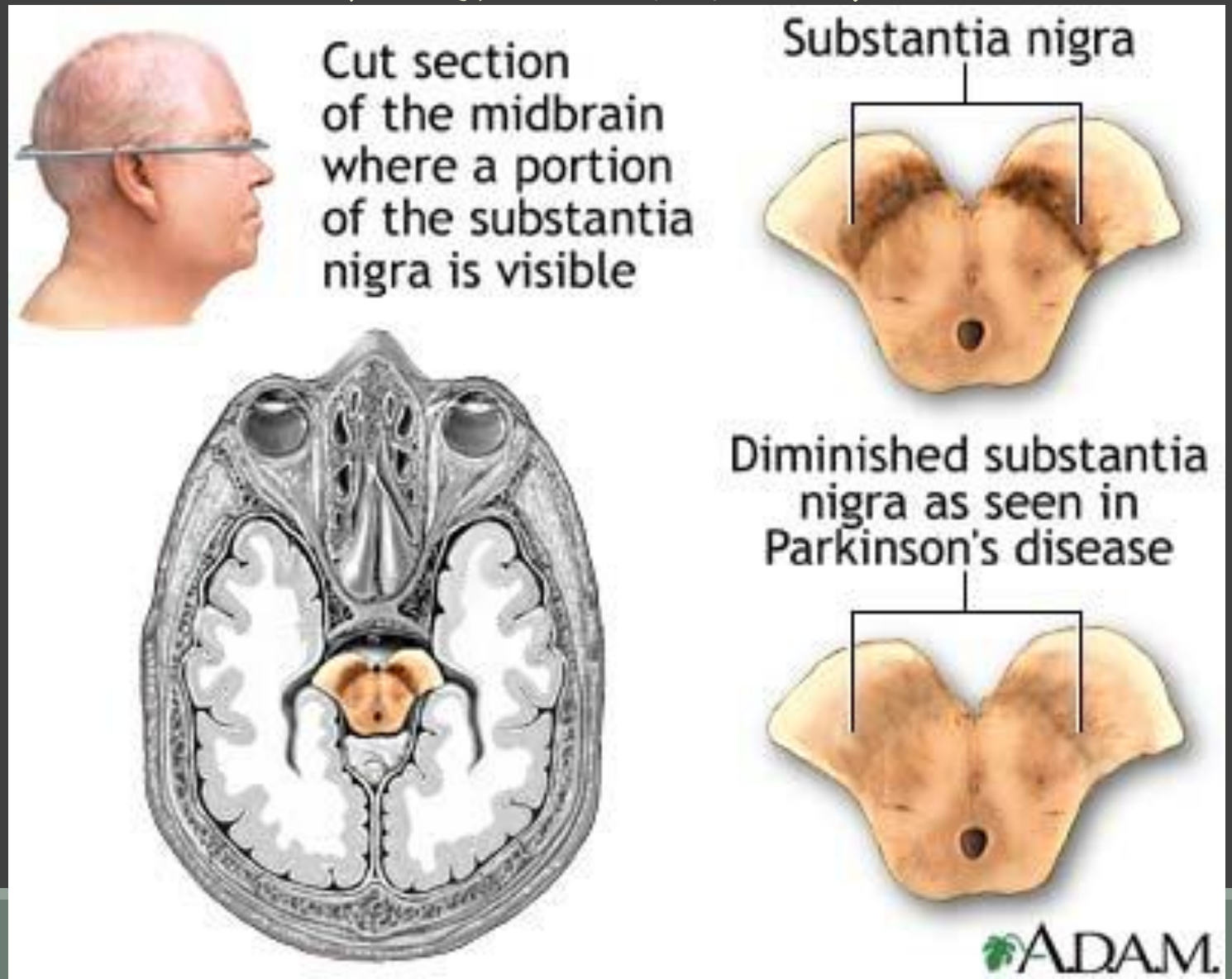
主要造成原因是因為腦內*黑質細胞*的退化

黑質細胞分泌*多巴胺*

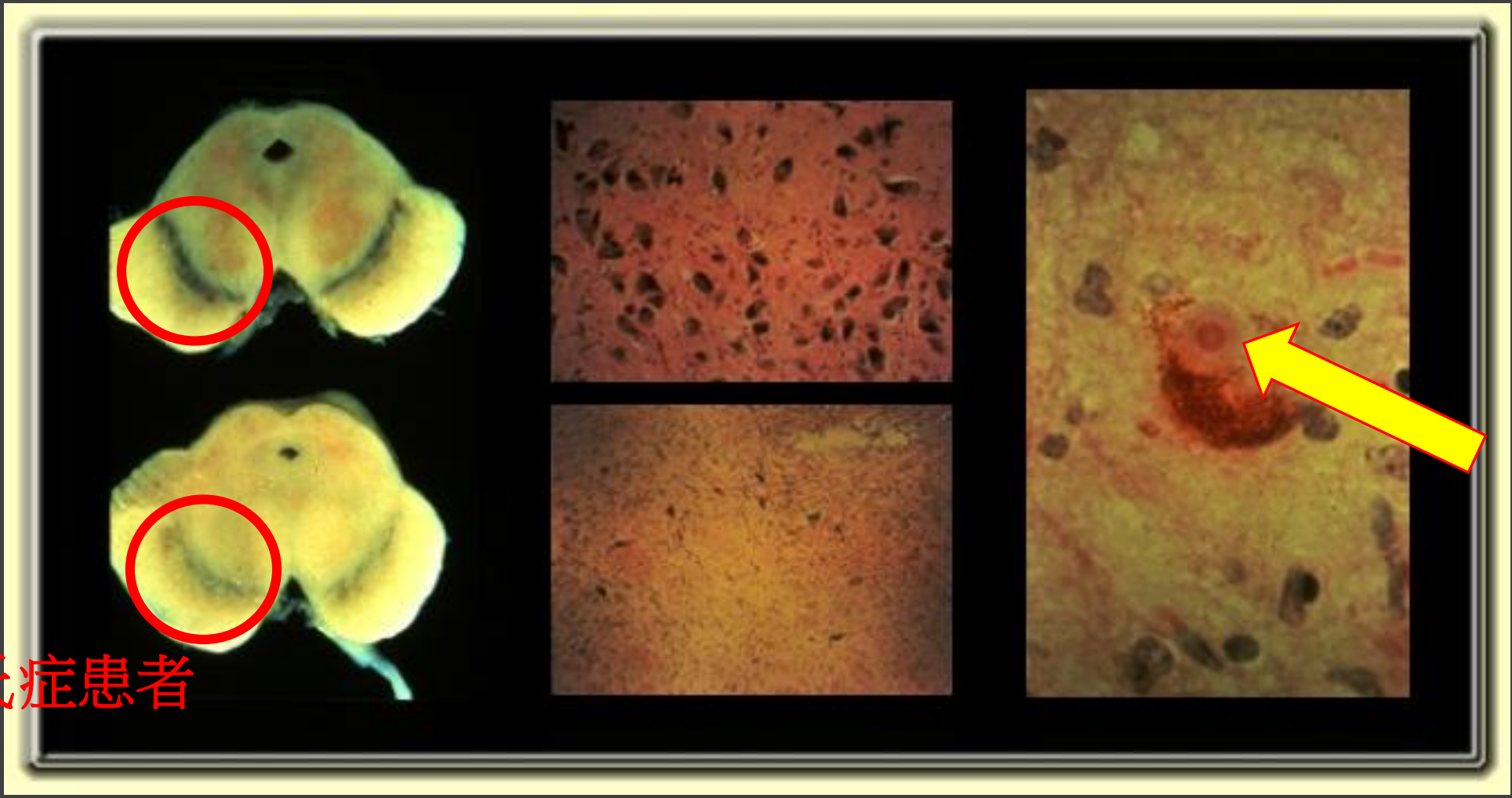
多巴胺的缺乏 造成動作上的困難

黑質細胞死亡時 都會有路易氏體的沉積

巴金森氏症的病理表現

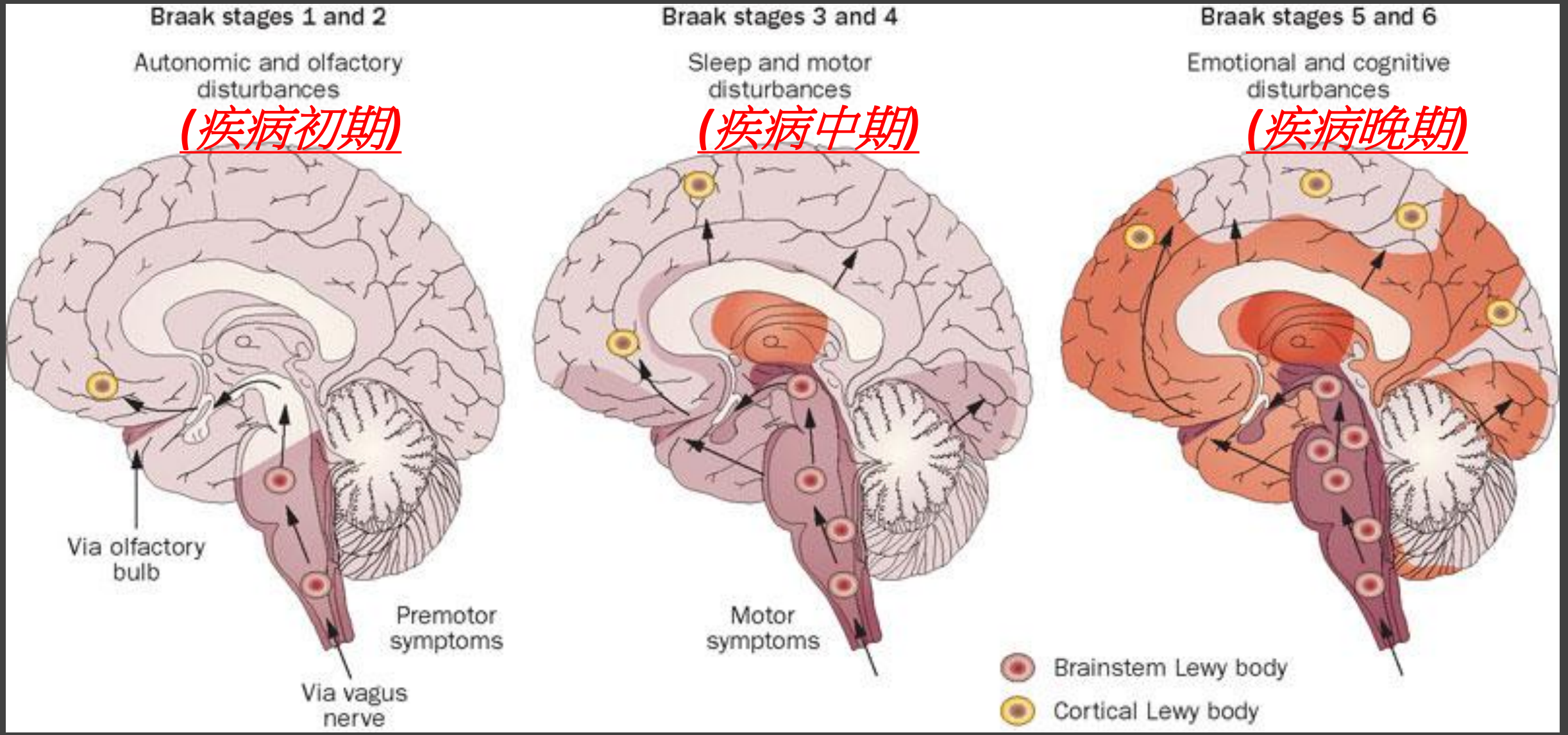

Cut section of the midbrain where a portion of the substantia nigra is visible
Substantia nigra
Diminished substantia nigra as seen in Parkinson's disease
A.D.A.M.

正常人

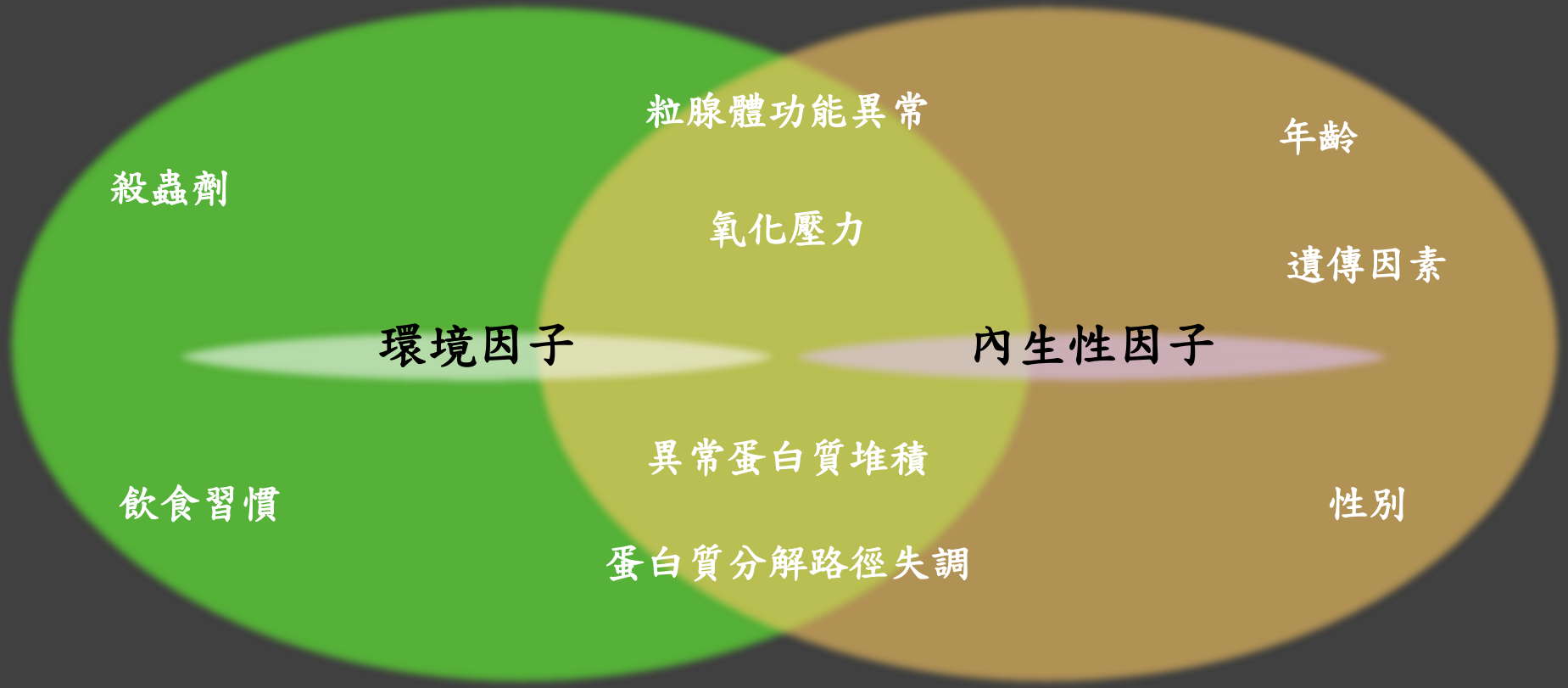


巴金森氏症患者

路易氏體


Braak stages 1 and 2
Autonomic and olfactory disturbances
(疾病初期)
Braak stages 3 and 4
Sleep and motor disturbances
(疾病中期)
Braak stages 5 and 6
Emotional and cognitive disturbances
(疾病晚期)
Via olfactory bulb
Premotor symptoms
Via vagus nerve
Motor symptoms
Brainstem Lewy body
Cortical Lewy body

巴金森氏症致病機轉


粒腺體功能異常
殺蟲劑
年齡
氧化壓力
遺傳因素
環境因子
內生性因子
異常蛋白質堆積
飲食習慣
性別
蛋白質分解路徑失調

環境因素

正常的腦部黑質細胞數量在50歲至90歲中每10年會減少百分之4.7至6.0。

Environmental Risk Factors (Neurotoxin)

- 農村的環境、從事農耕、農藥曝露
- 喝井水
- 重金屬 (錳)
  - n-hexane (paints, glues, gasolines)
  - MPTP

C型肝炎病毒帶原者(2016)

Gibb et al. Journal of Neurol Neurosurg Psychiatry 1991:54:388-396.

遺傳因素

雖然大多數的病人沒有家族遺傳史, 但其中仍有 5-10% 的病人具有家族遺傳史。

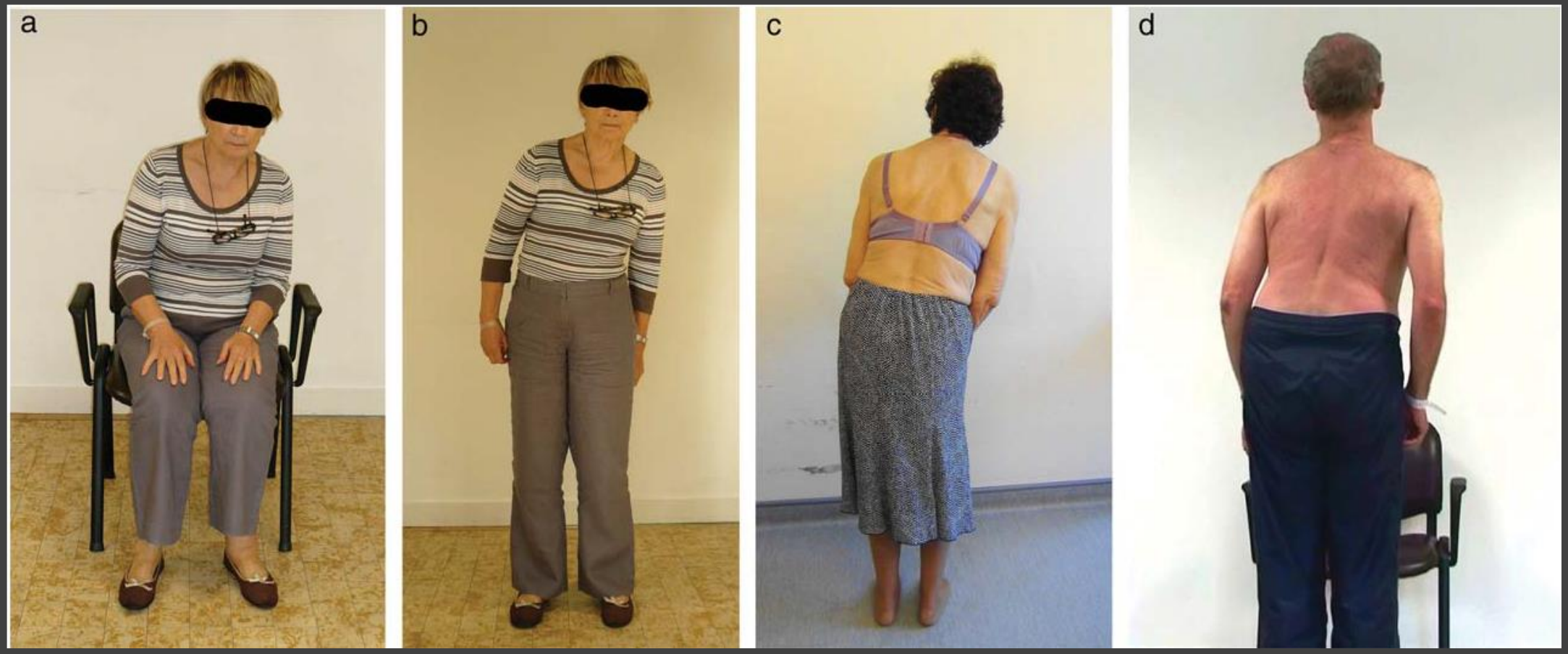
最近幾年的研究發現某些基因的突變會導致遺傳性巴病的發生，目前已有數個基因的突變已被證實是引起少數遺傳性巴病的致病因，這些發現證明巴病為一多種基因異常之複雜性退化症，也強調了環境因子和遺傳因子之間的相互作用在巴病致病機轉中的重要性。

困難處理的巴金森症動作障礙

凍僵步態 (Freezing of Gait)

2015 Lancet Neurology

Pisa Syndrome



異動症(Dyskinesia)

“非”動作障礙的症狀

便祕

睡眠問題

譫妄

憂鬱症

焦慮症

失智症

女兒

兒子

他們是誰?

幻覺 妄想 譫妄

巴金森失智症

幻覺: 視幻覺較多

很多小孩子、小動物在房間裡、把物品誤認為人臉、看到有人站在身邊

(把燈打開可以解決一些狀況)

聽幻覺: 一些單一的聲音、或者是人的對話的聲音

妄想: 懷疑伴侶不忠、將幻覺誤認為真的感到害怕

認知功能: 執行能力變差、無法解決多步驟的問題、視覺空間感變差、記憶力(影響比例較少)

其他非運動障礙

夜尿: 男性常被誤認為攝護腺肥大

姿勢性低血壓: 常出現”眼睛上吊暈倒” 或 “一站起來時眼前突然一片黑”

睡眠障礙 : 睡覺時拳打腳踢、做很多夢

憂鬱、焦慮

嚴重便秘 : 無力解便 或 糞便很硬很少

什麼叫非典型巴金森氏症?

1. 兩側同時出現症狀
2. 進展快速 從症狀出現到無法走路可能只有2-4年的時間
3. 對藥物的反應效果不佳
4. 平衡感特別差、早期出現的認知功能下降或幻覺
5. 早期出現頻繁跌倒

非典型巴金森症

可能診斷:

(1) 多神經系統退化症 (Multiple Systemic Atrophy)
伴隨嚴重的姿勢性低血壓、走路不平衡有小腦症狀、大小便失禁

(2) 進行性上眼神經核麻痺症 (Progressive Supranuclear Palsy)

眼睛無法往下看、下樓梯困難、早期出現往後跌倒的情形、早期吞嚥困難

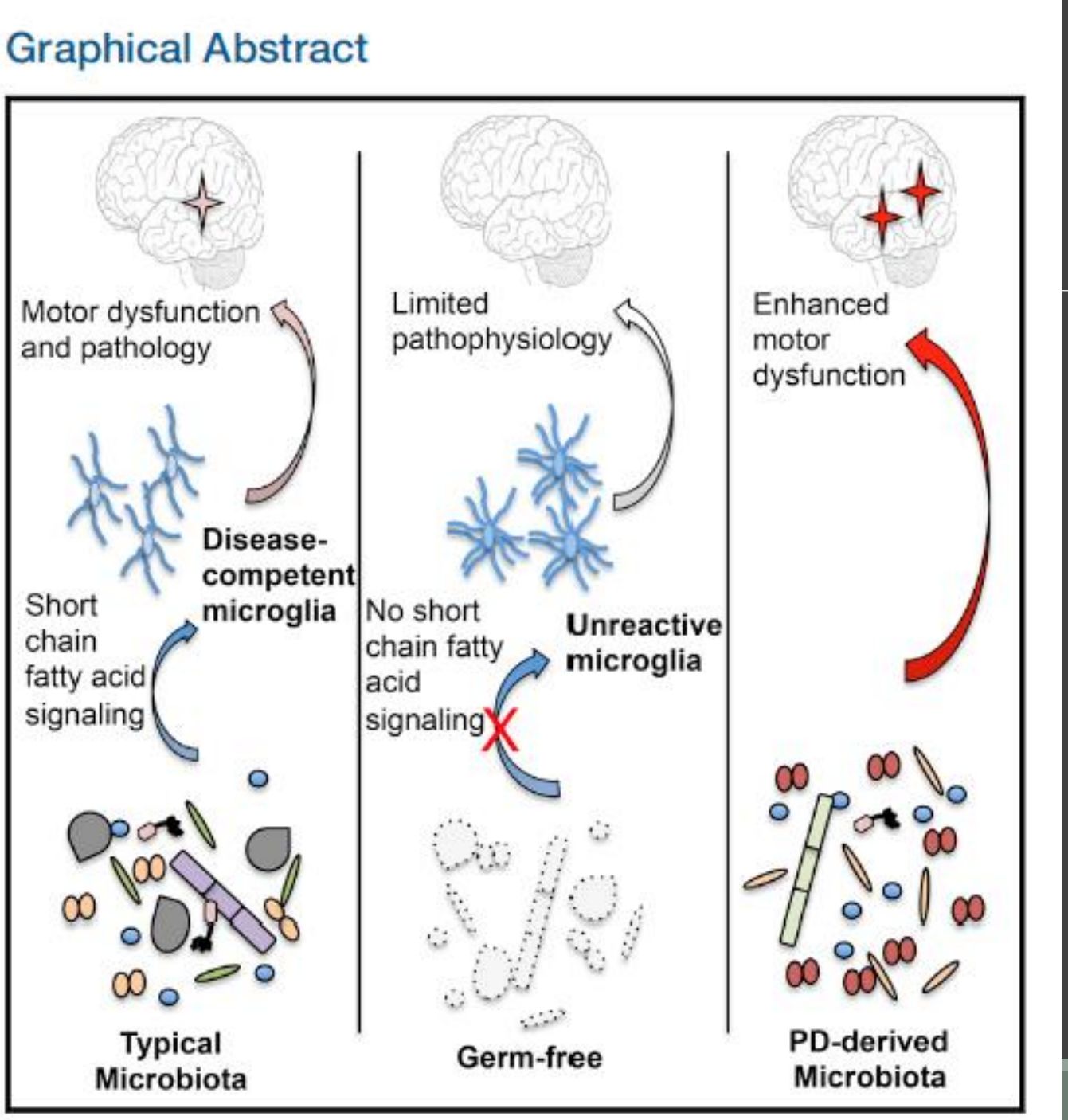
(3) 皮質基底核退化症 (Cortico Basal Ganglion Syndrome)

非常顯著的不對成性、僵硬伴隨肌張力異常、皮質感覺異常、反射性肌躍症

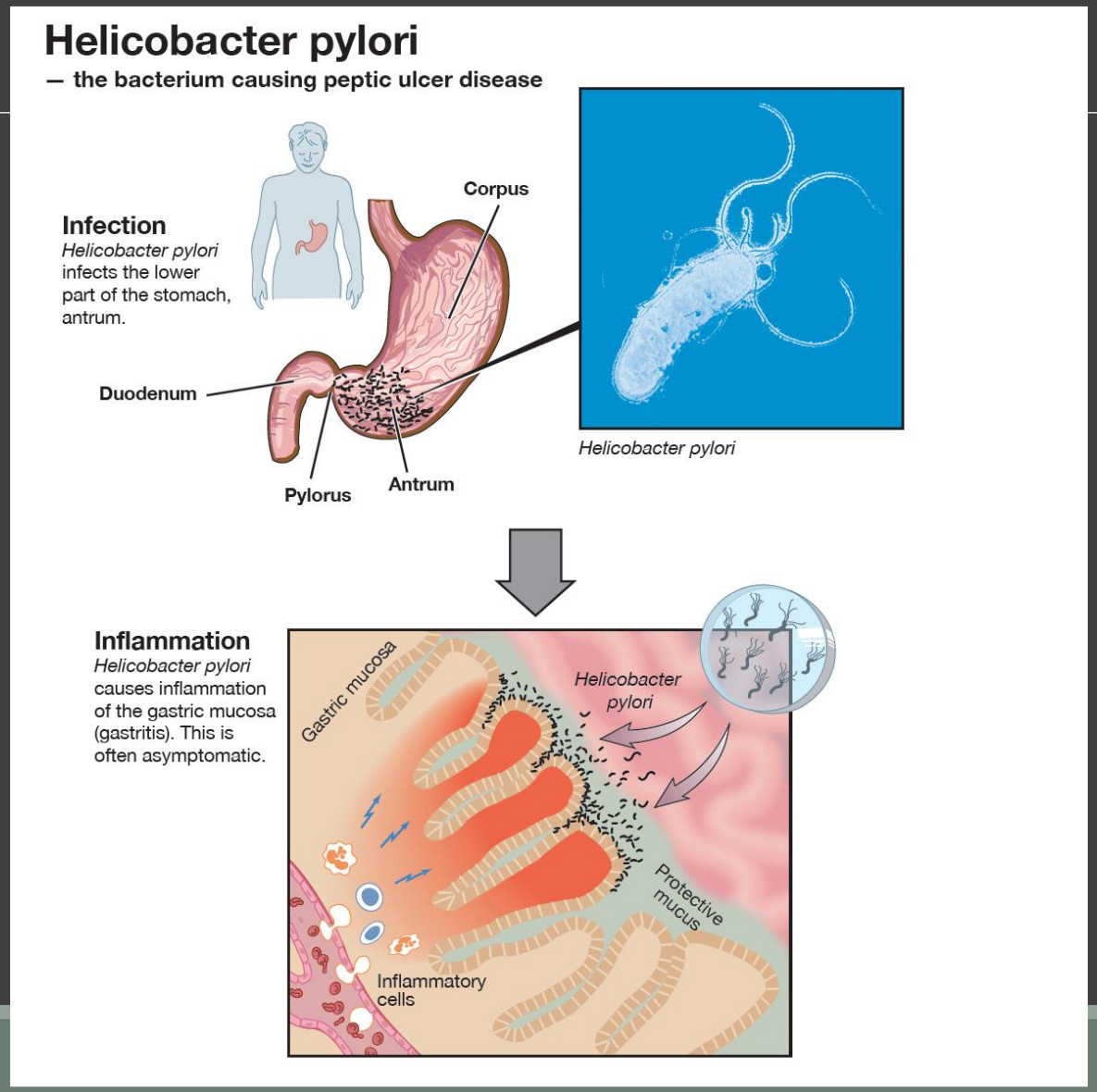
(4) 血管性巴金森症 (Vascular Parkinsonism)

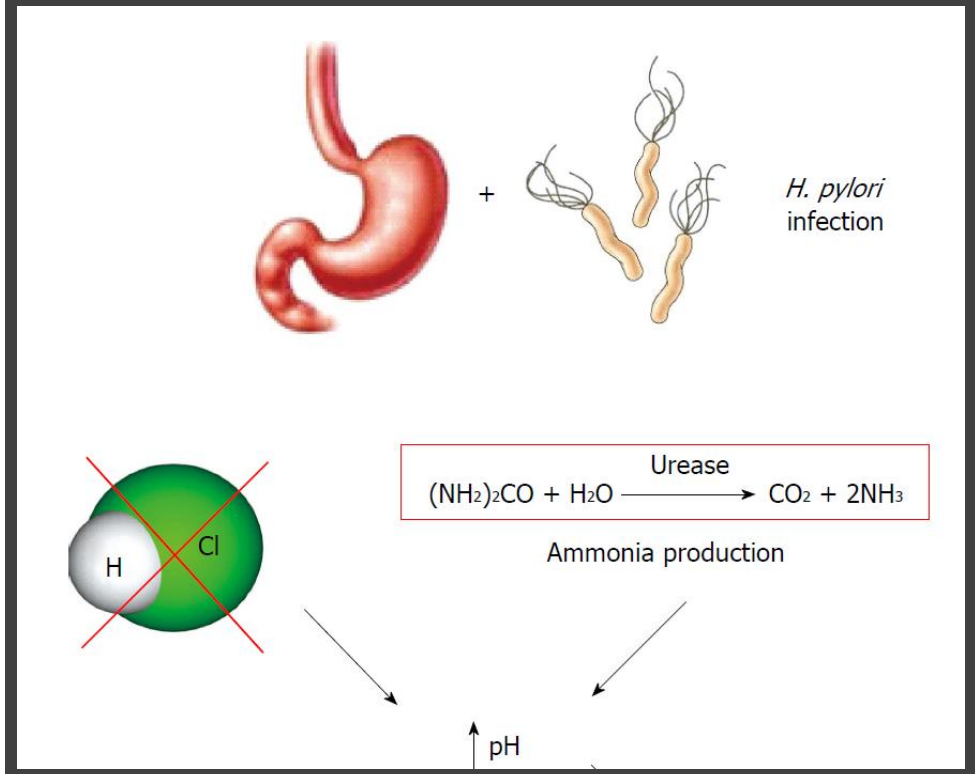
多次中風或多種中風危險因子、腳步難以邁開、雙腳寬站姿站立

醫生，已


Graphical Abstract
Motor dysfunction and pathology
Disease-competent microglia
Short chain fatty acid signaling
Typical Microbiota
Limited pathophysiology
No short chain fatty acid signaling
Unreactive microglia
Germ-free
Enhanced motor dysfunction
PD-derived Microbiota

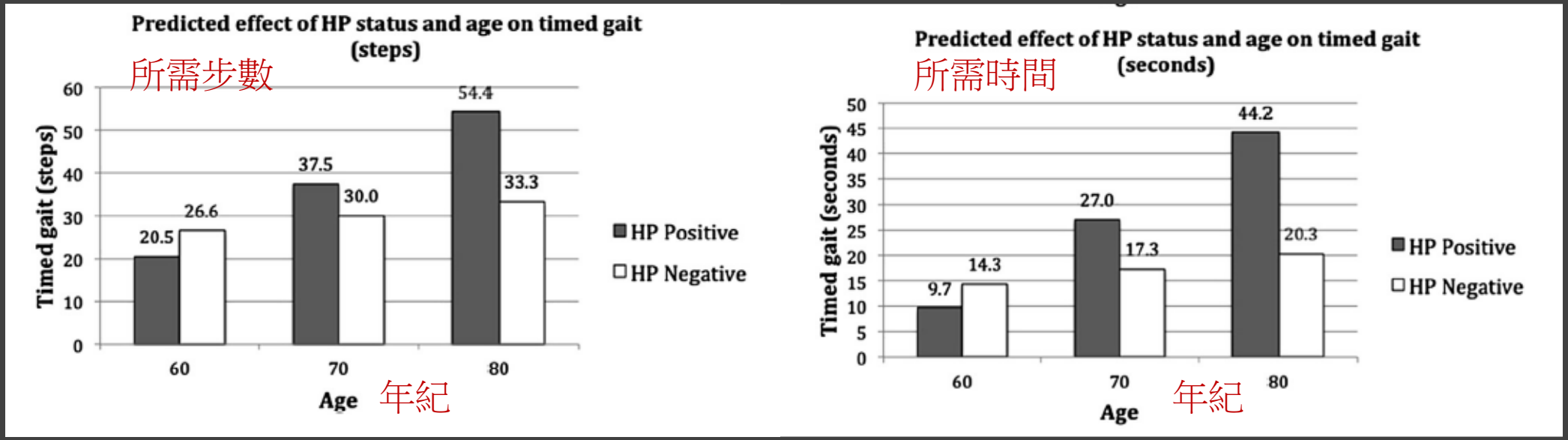
腸內細菌與巴金森氏症


Helicobacter pylori
— the bacterium causing peptic ulcer disease
Infection
Helicobacter pylori infects the lower part of the stomach, antrum.
Corpus
Duodenum
Pylorus
Antrum
Helicobacter pylori
Inflammation
Helicobacter pylori causes inflammation of the gastric mucosa (gastritis). This is often asymptomatic.
Gastric mucosa
Helicobacter pylori
Protective mucus
Inflammatory cells


+
H. pylori infection
H
Cl
Urease
(NH2)2CO + H2O → CO2 + 2NH3
Ammonia production
pH

胃裡的幽門桿菌與巴金森氏症的關係 What dose H.Pylori do for PD?

有幽門桿菌感染的巴金森氏症患者 走路的狀況會比較差



存在於巴金森氏症的腸胃道菌種

- 巴金森的病患的腸道內有比正常人低量的普雷沃氏菌群(Prevotellaceae microbiome)
- 當腸桿菌科(Enterobacteriaceae)在腸道裡越豐富的時候 病患越容易出現僵硬型而非顫抖型的巴金森氏症症狀

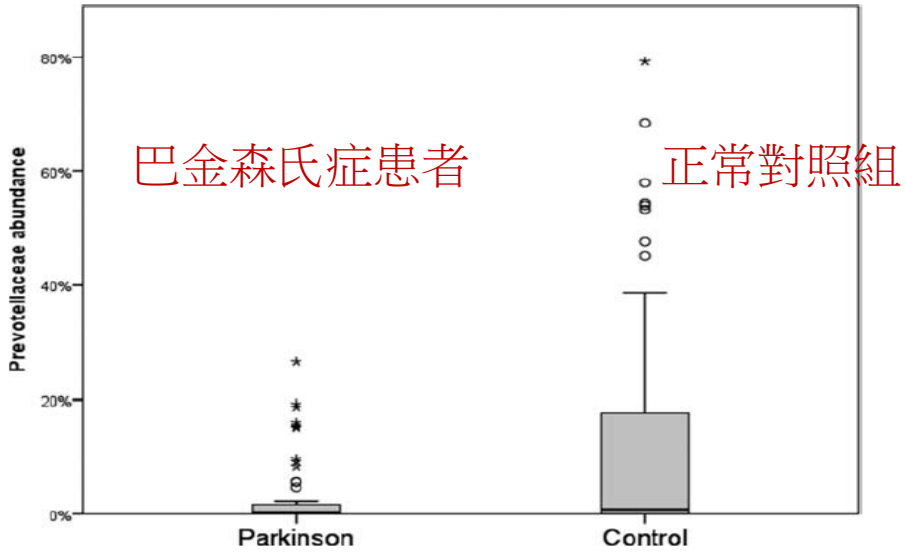


FIG. 1. Box plots showing the distributions of Prevotellaceae abundance in both study groups. Black horizontal lines indicate the median values and the boxes around them delineate the IQR. Whiskers extend to the highest value within 1.5 IQR of the upper quartile. Circles represent outliers beyond the whisker limit and asterisks represent extreme outliers beyond 3 IQR of the upper quartile. High levels of Prevotellaceae were rare in the PD group whereas low levels were found in both groups. Median [IQR]: Parkinson 0.16% [0.00%-1.66%]; Control: 0.77% [0.00%-18.18%]

巴金森氏症與腸胃道菌種的關係

陳醫師解答:

- 幽門桿菌與巴金森氏症得病與否目前不認為有直接關聯
- 若巴金森氏症病人在中後期病程有藥物波動現象，並伴隨有胃痛、胃潰瘍等症狀，可能與幽門桿菌有關
- 菌種種類與疾病關係: 未知因果! 刻意改變飲食 並不會輕易改變腸內菌種!

結論:

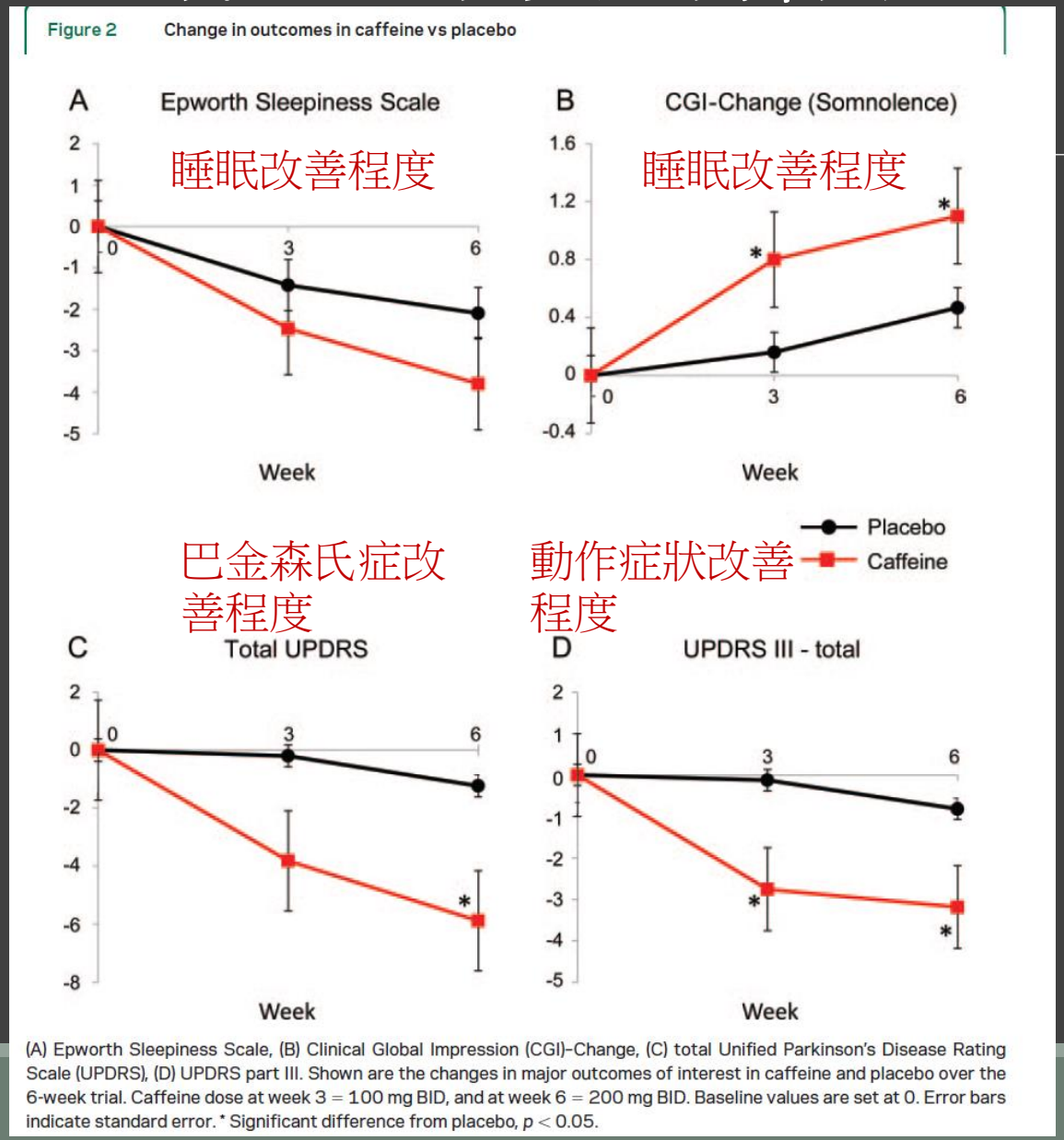
腸胃道細菌引起巴金森症? 目前證據不足!

有藥物波動現象的病人若有伴隨胃潰瘍情形，建議做幽門桿菌檢查與治療

長期改變飲食策略有無助於改變腸道內菌種 目前未知 需等待進一步研究結果

咖啡因有沒有幫助?

咖啡因有沒有幫助?



1. 咖啡因用來治療巴金森氏症患者早上的嗜睡狀態 **效果不理想**
2. 從研究結果顯示 咖啡因可以讓巴金森氏症患者**臨床的症狀改善約3-4分**
3. 使用咖啡因的量大約是每天100-200毫克 持續六周
4. 透過的機轉是藉由Adenosine A2A 受體拮抗

咖啡因有沒有幫助?

陳醫師解答:

- 一杯中杯美式咖啡約為150毫克咖啡因 需要每天一杯 連續至少六周
- 但是咖啡因會造成胃酸分泌 對長期***胃部不適***的病人較不好
- 但必須要注意咖啡因可能會造成***顫抖更嚴重***、並且可能會有耐受性的產生
- 結論:

可能有幫助 建議酌量攝取即可
不用刻意飲用

血中的尿酸與巴金森氏症的關係

http://nuoyuann.pixnet.net/blog/post/102990439

血中的尿酸是否應該刻意提高?

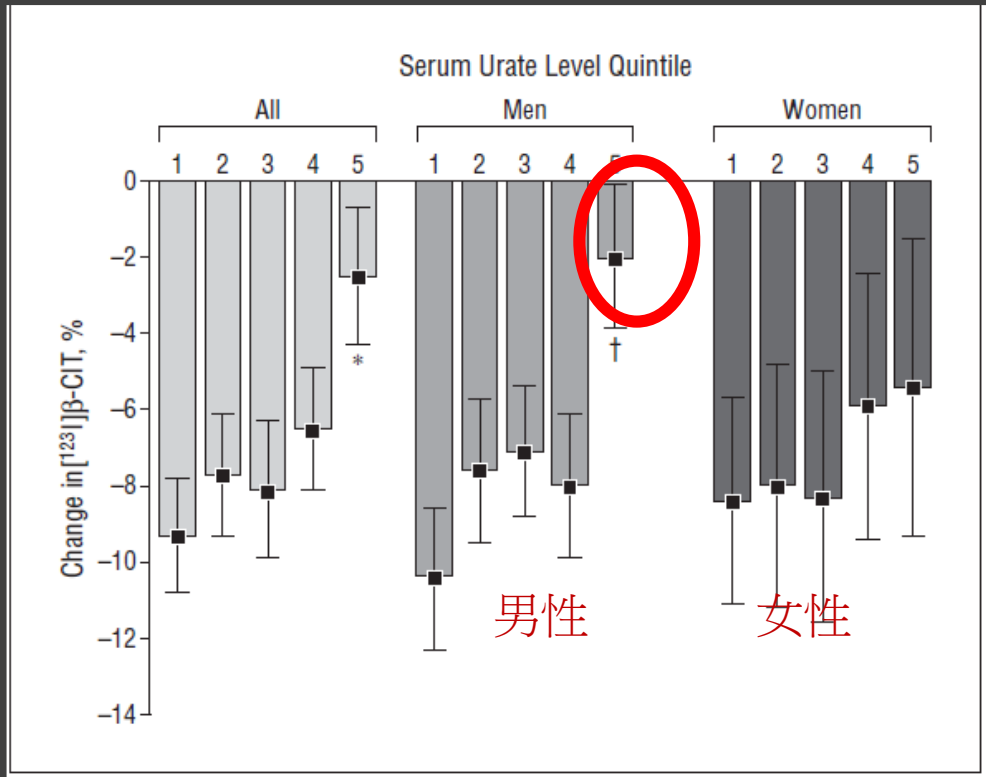


Figure 2. Age-adjusted percentage of change in striatal iodine I 123–labeled 2-beta-carbomethoxy-3-beta-(4-iodophenyl)tropane ([^{123}I]β-CIT) uptake according to overall and sex-specific quintiles of baseline serum urate level. Median serum urate level by quintiles (1-5) in milligrams per deciliter: all: 3.8, 4.8, 5.5, 6.3, and 7.5; men: 4.4, 5.3, 6.0, 6.6, and 7.8; and women: 3.1, 4.0, 4.5, 5.2, and 6.6. *$P<.05$; †$P<.001$ compared with corresponding quintile 1. P for linear trend: all, $P=.002$; men, $P=.001$; and women, $P=.43$. Error bars represent the standard error of the mean.

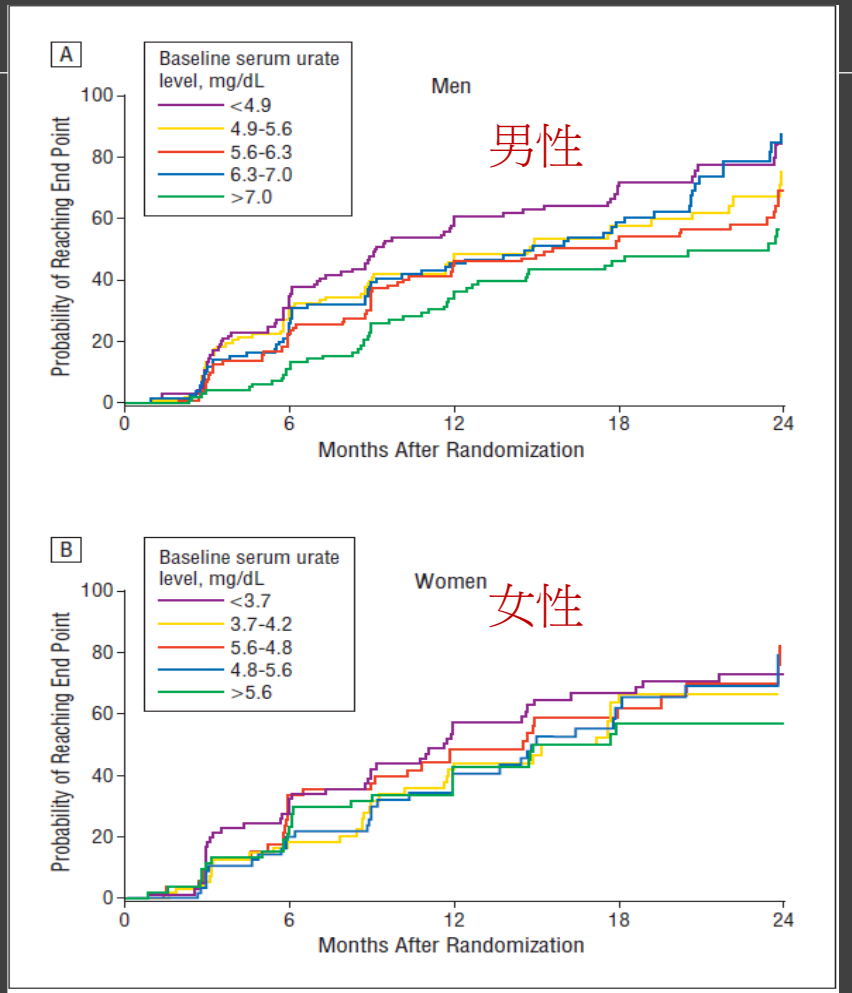


Figure 1. Kaplan-Meier estimates of the cumulative probability of reaching the end point by 24 months of follow-up according to sex-specific quintiles of baseline serum urate level. A, Men. B, Women. Log-rank tests: $P=.001$ in men; $P=.47$ in women. At 24 months, the sample size was 46 men and 21 women.

血中的尿酸是否應該刻意提高?

陳醫師解答:

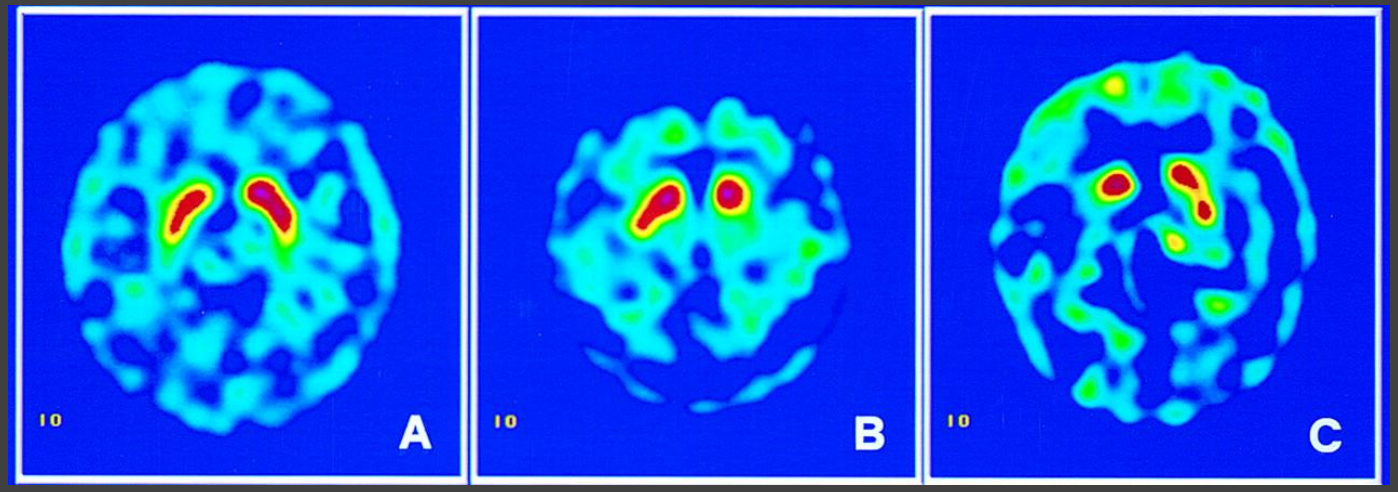
- 尿酸在7.8mg/dL以上 相對應的影像學變化退化較少
- 有性別上的差異 男性較女性明顯
- 高尿酸會引致痛風的發生 並且提高心血管、腦血管疾病的發生率

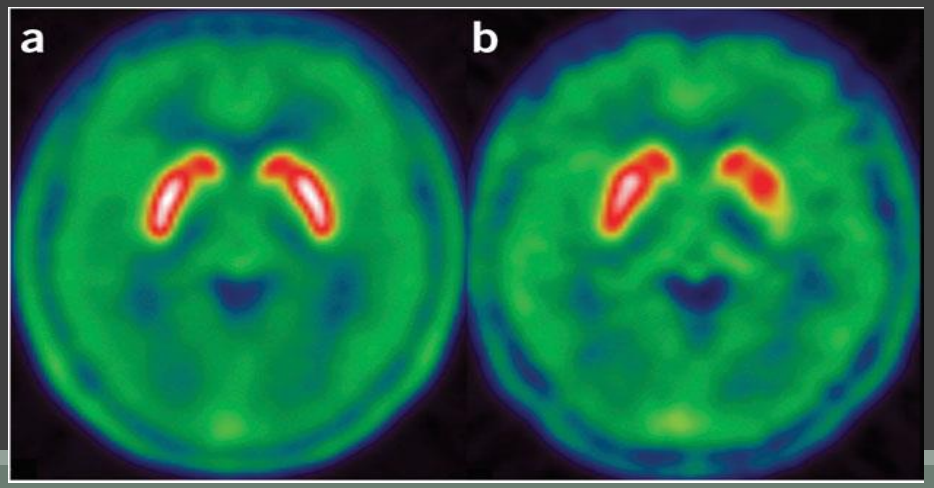
結論:

未知因果 不確定有無幫助
必須等待口服補充的研究結果(2020年)

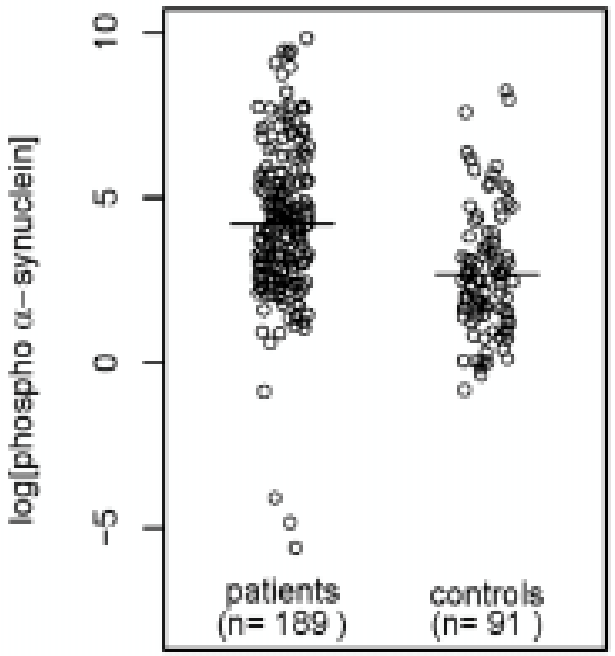
目前不建議刻意提高

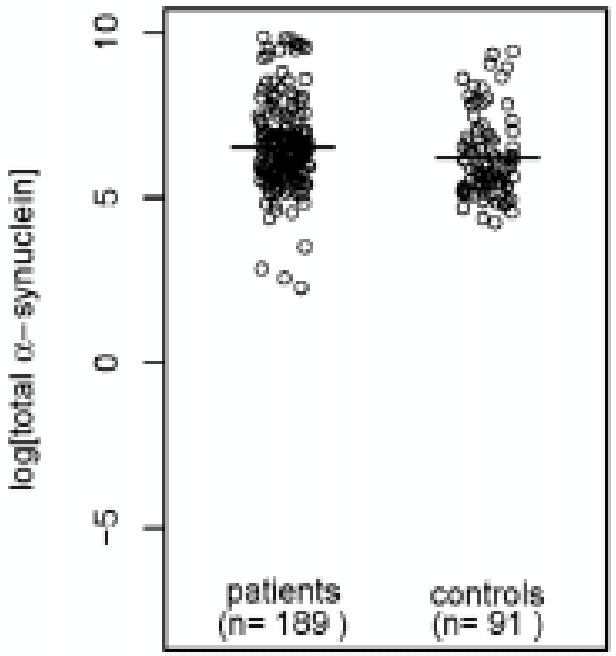
正子掃描

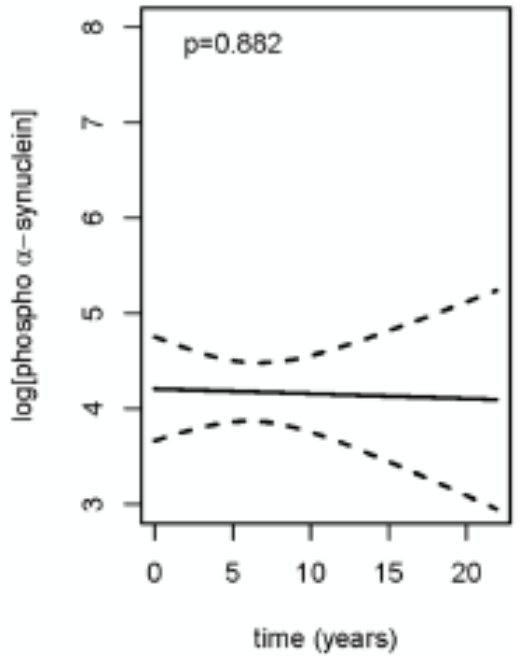


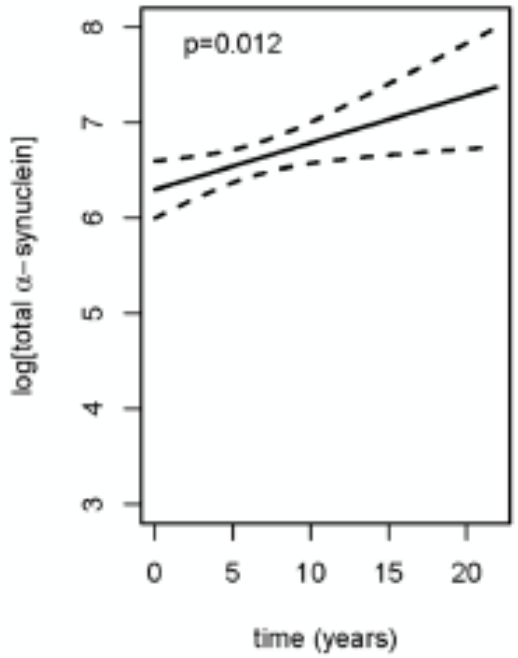


嘗試從血液中的α-synuclein來診斷巴金森氏症

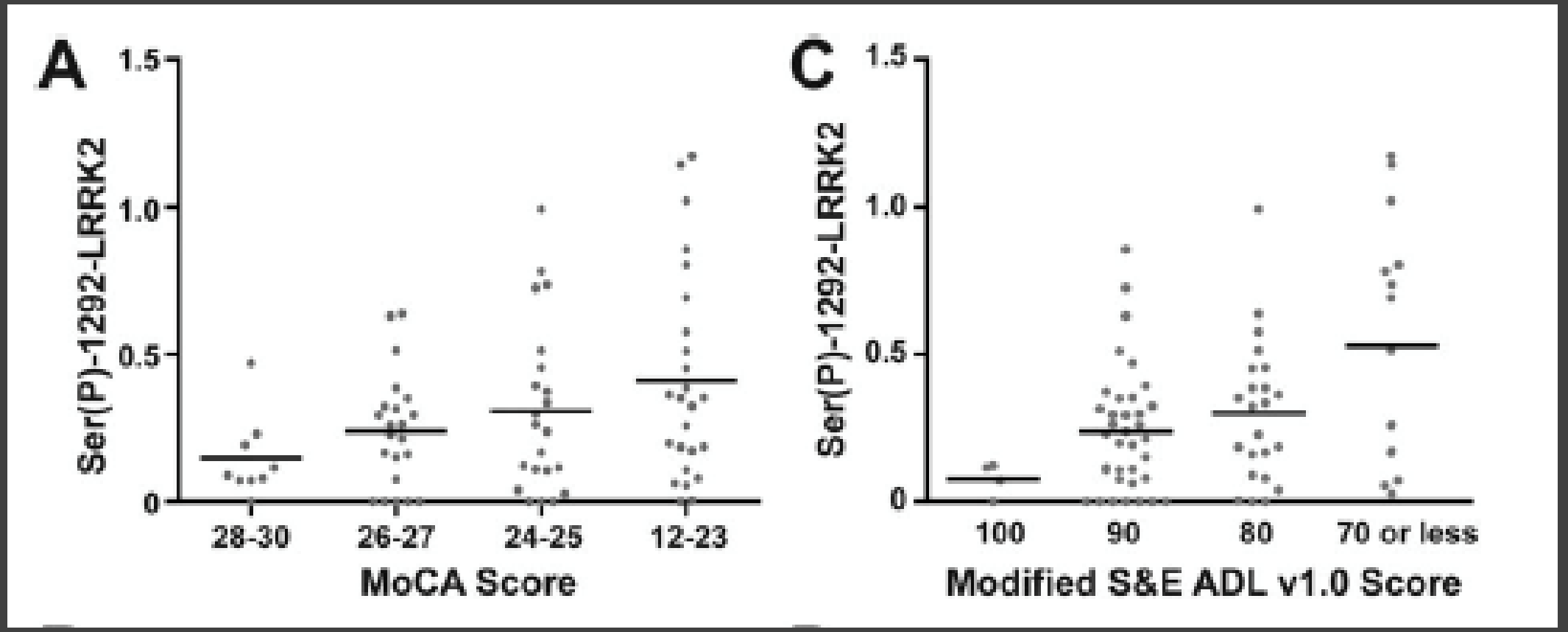








利用尿液中LRRK-2 Exosomes去辨別疾病嚴重度



巴金森氏症新治療藥物

CVT-301

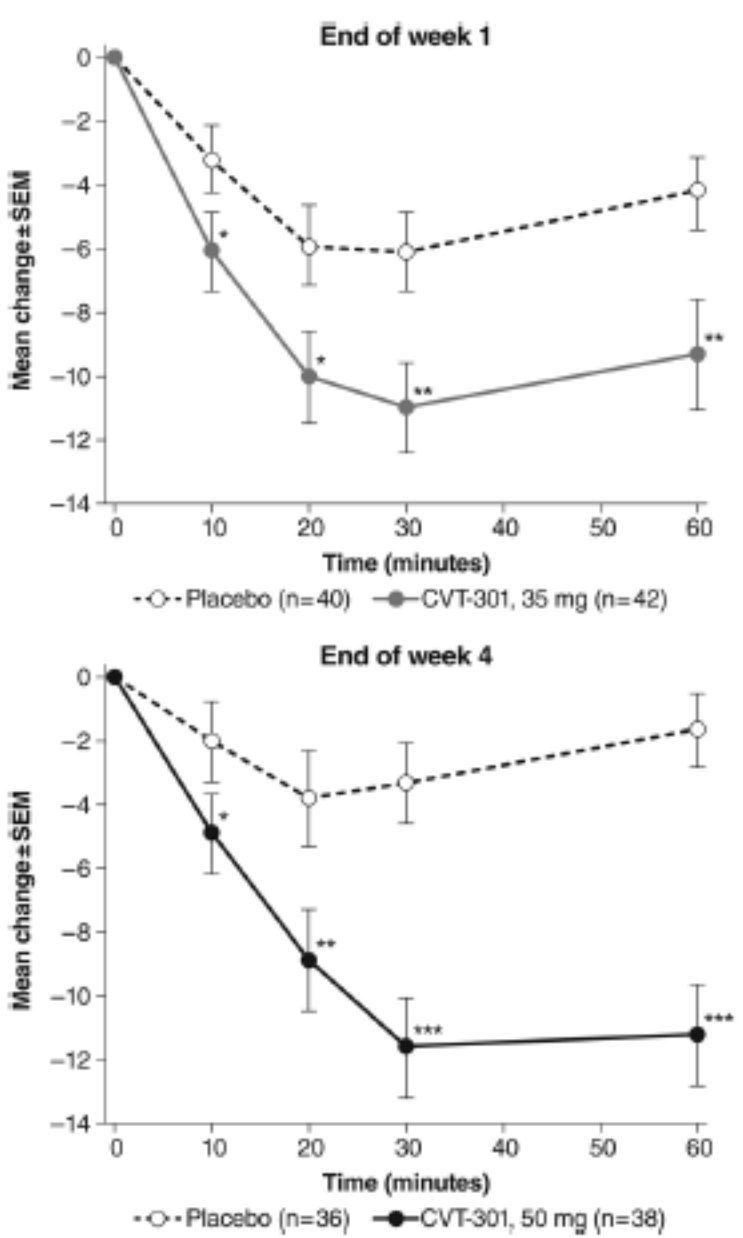


FIG. 2. Mean serial UPDRS Part III score change for 2 CVT-301 dose levels versus placebo (mITT population). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs placebo, MMRM. mITT, modified intent to treat; MMRM, mixed model for repeated measurements; SEM, standard error of the mean; UPDRS, Unified Parkinson's Disease Rating Scale.

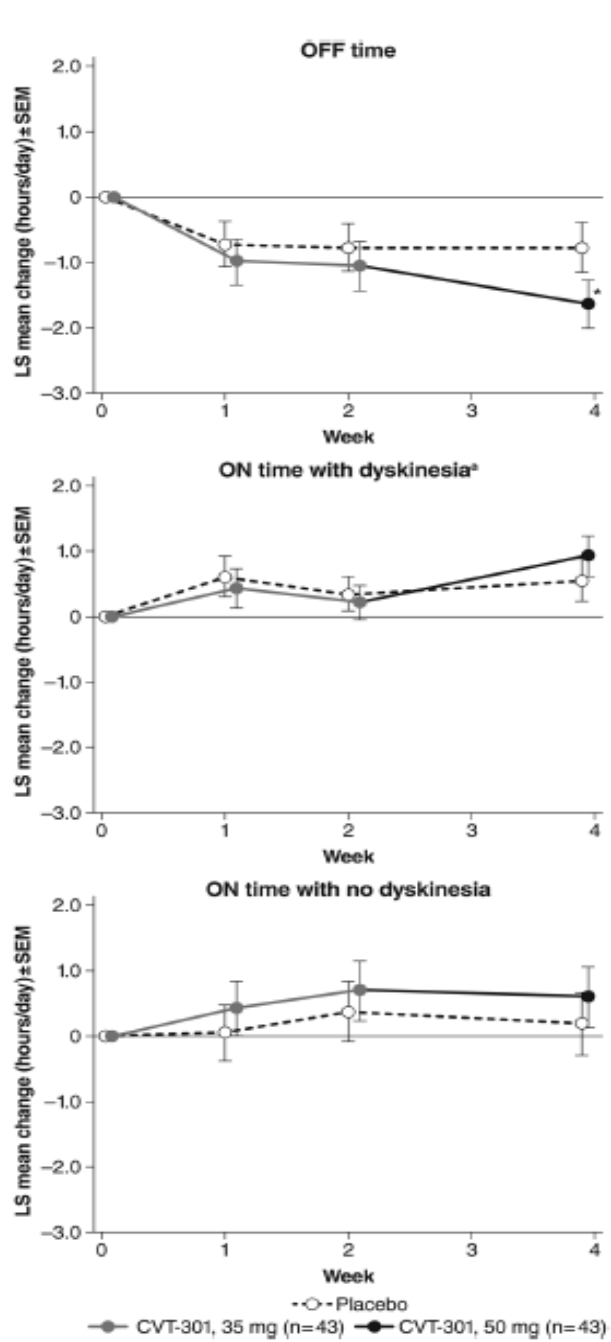


FIG. 3. LS mean change in OFF time, in ON time with dyskinesia, and in ON time with no dyskinesia throughout the study, based on 3-day averages from PD diary entries (mITT population). *$P < 0.05$ vs placebo. MMRM. [a]Troublesome or nontroublesome. LS, least squares;

Amantadine Extended Release for Levodopa-Induced Dyskinesia

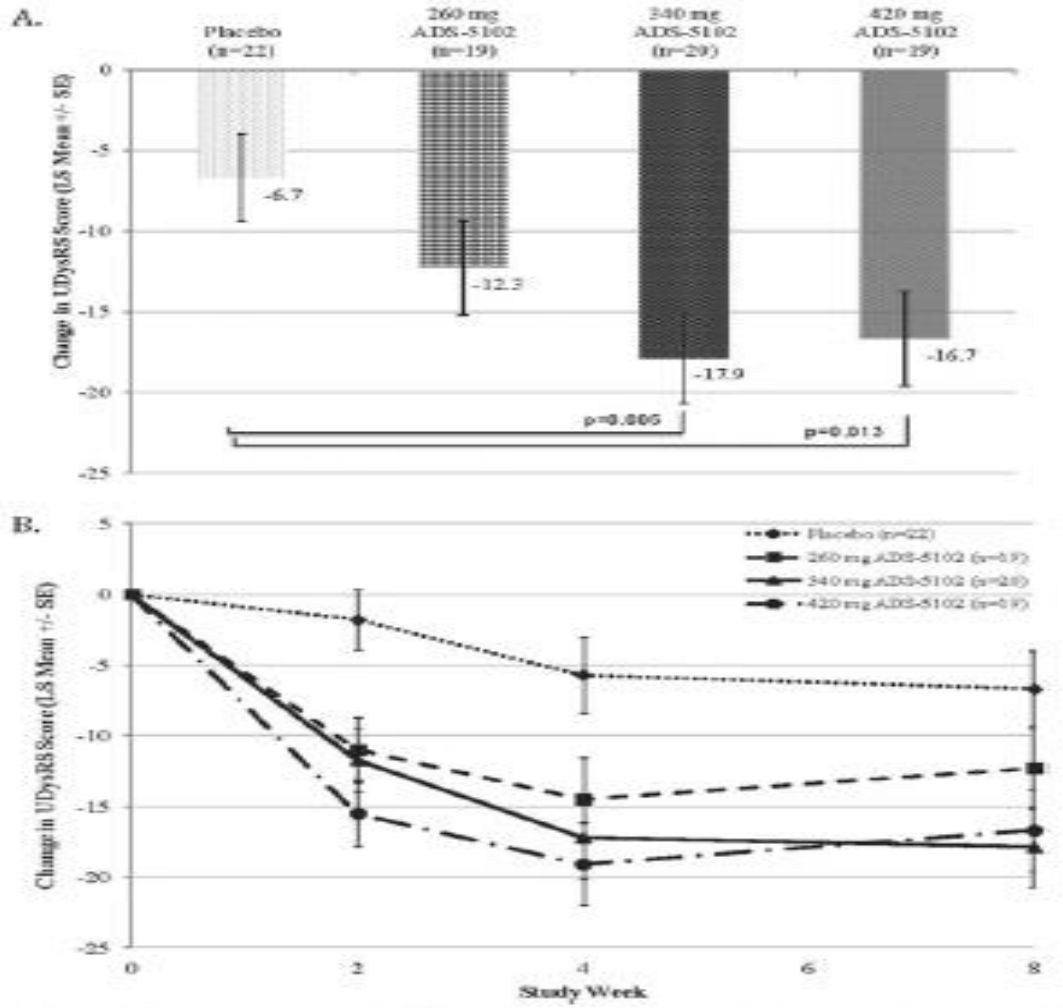
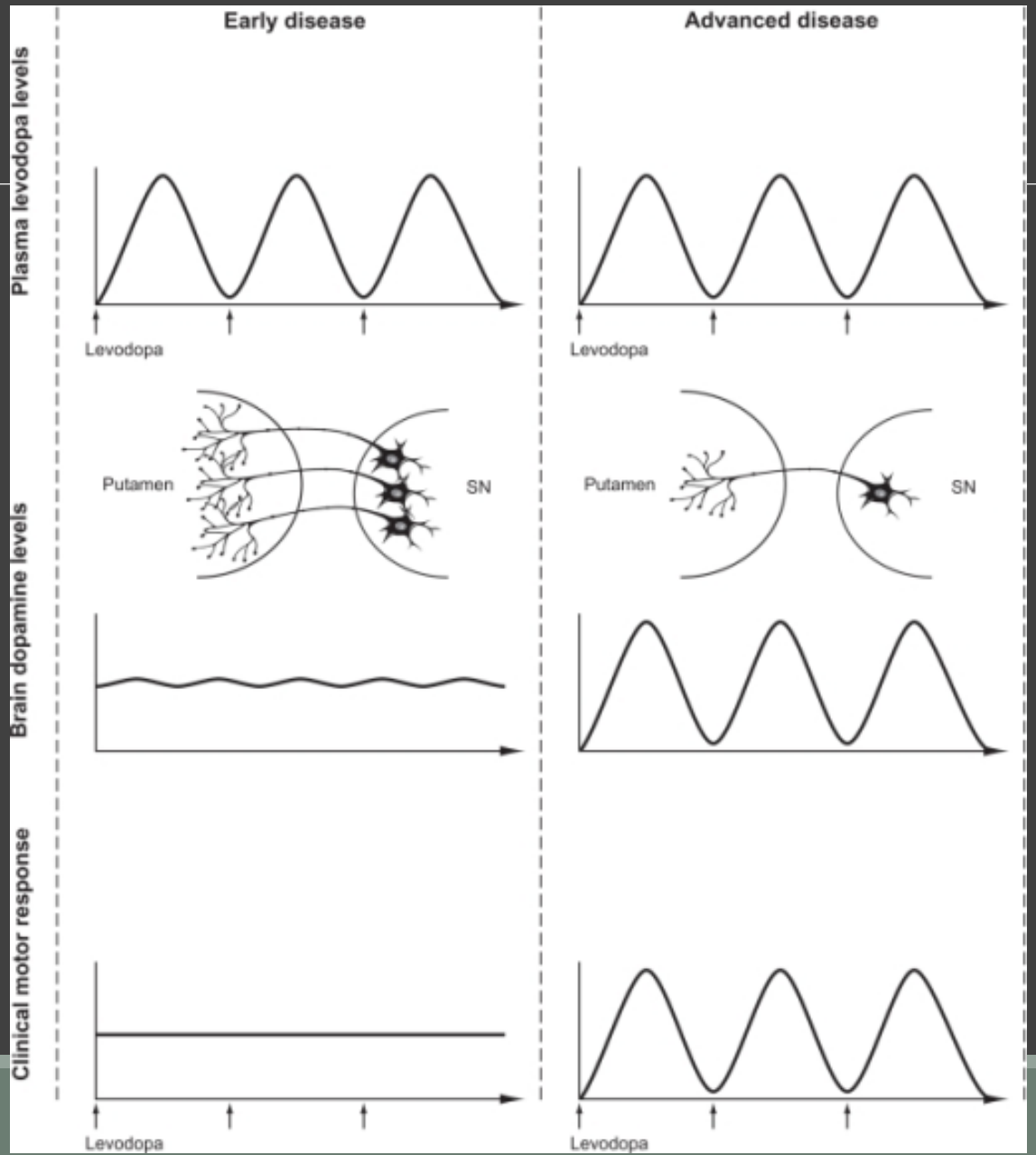


FIG. 2. Change in Unified Dyskinesia Rating Scale (UDysRS) total

	LS Mean Treatment Difference vs. Placebo (95% CI)		
	260 mg ADS-5102 ($n = 19$)	340 mg ADS-5102 ($n = 20$)	420 mg ADS-5102 (n = 19)
nesia, h	3.3 (1.1, 5.5) p=0.004	3.0 (0.8, 5.2) p=0.008	2.7 (0.5, 5.0) p=0.018
ia, h	−1.3 (−3.1, 0.6) p=0.169	−1.8 (−3.6, 0.0) p=0.055	−2.8 (−4.6, −0.9) p=0.0
	−1.1 (−3.7, 1.5) p=0.408	−2.1 (−4.8, 0.5) p=0.117	−3.1 (−5.8, −0.5) p=0.0
	−1.3 (−2.7, 0.1) p=0.074	−0.9 (−2.3, 0.5) p=0.199	0.1 (−1.4, 1.5) p=0.934
	−0.8 (−1.8,0.2) p=0.099	−0.4 (−1.4,0.5) p=0.367	−0.3 (−1.2,0.7) p=0.573
III, IV)	−2.5 (−6.0, 0.9) p=0.147	−5.2 (−8.7, −1.7) p=0.004	−6.4 (−9.8, −2.9) p<0.0
	−0.7 (−2.9, 1.5) p=0.520	−2.4 (−4.6, −0.3) p=0.026	−3.4 (−5.6, −1.2) p=0.0
ne spent with dyskinesia	−0.2 (−0.8, 0.5) p=0.630	−0.6 (−1.2, 0.1) p=0.100	−0.6 (−1.3, 0.0) p=0.05
unctional impact of dyskinesia	−0.8 (−1.4, −0.2) p=0.014	−1.0 (−1.6, −0.4) p=0.002	−1.3 (−2.0, −0.7) p<0.0
ed)	1.2 (−7.7, 10.1) p=0.786	−2.2 (−11.2, 6.9) p=0.636	1.7 (−7.2, 10.6) p=0.70
	0.2 (−0.6, 1.0) p=0.630	−0.3 (−1.1, 0.5) p=0.431	0.3 (−0.5, 1.0) p=0.522
	−0.3 (−8.7, 8.0) p=0.942	−3.4 (−11.5, 4.7) p=0.406	2.2 (−5.9, 10.3) p=0.59

Continuous Drug Delivery Concept

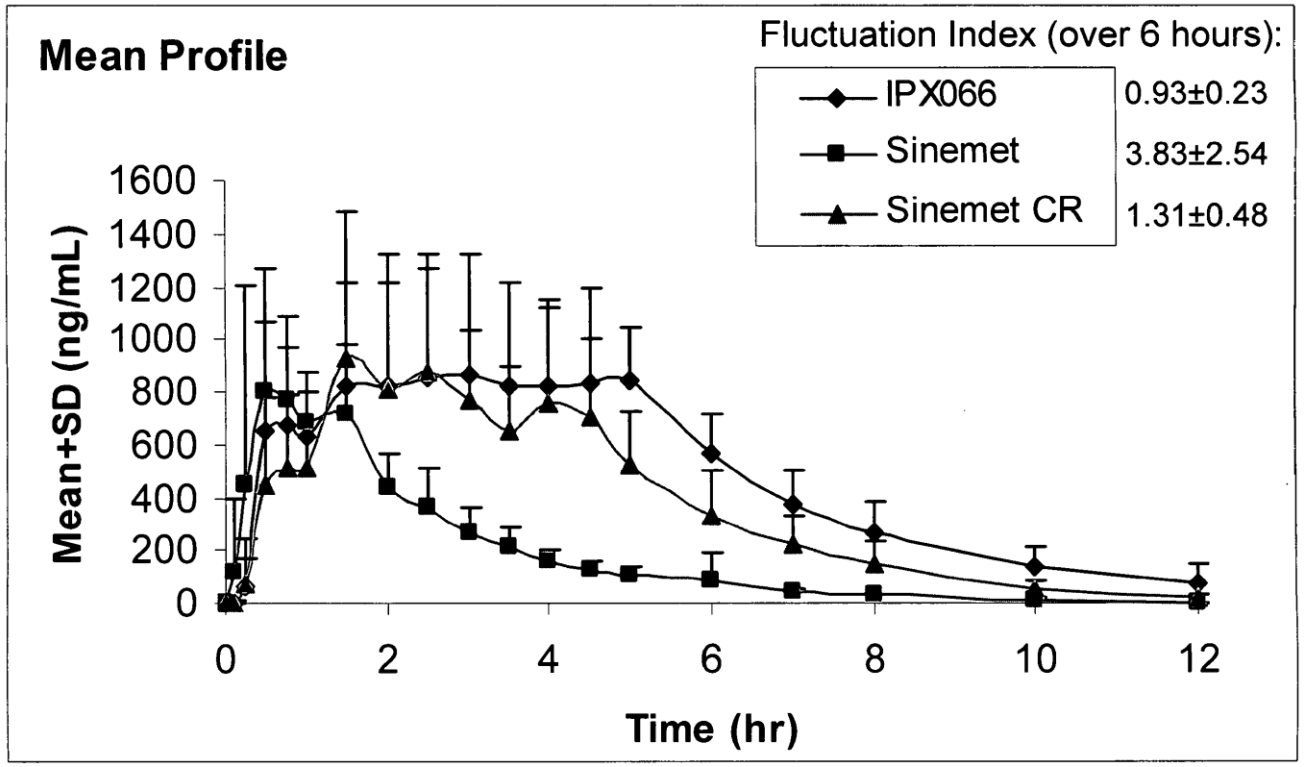


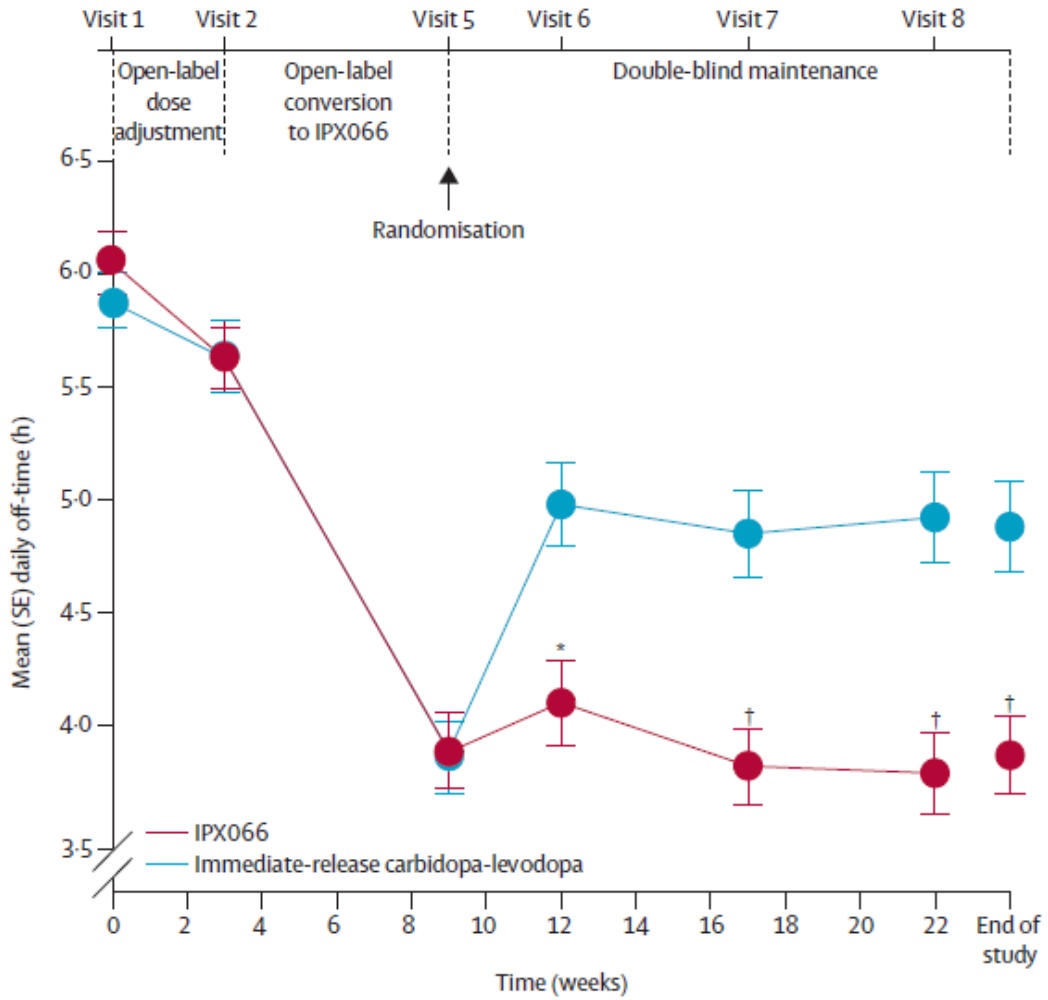
IPX066 (Rytary)

長嘯持續型的左多巴胺

2015 一月 已經由美國食品藥物管理局核准通過為巴金森氏症治療用藥

IPX066 Plasma Profiles vs. IR or CR





re 2: Mean daily off-time throughout the study

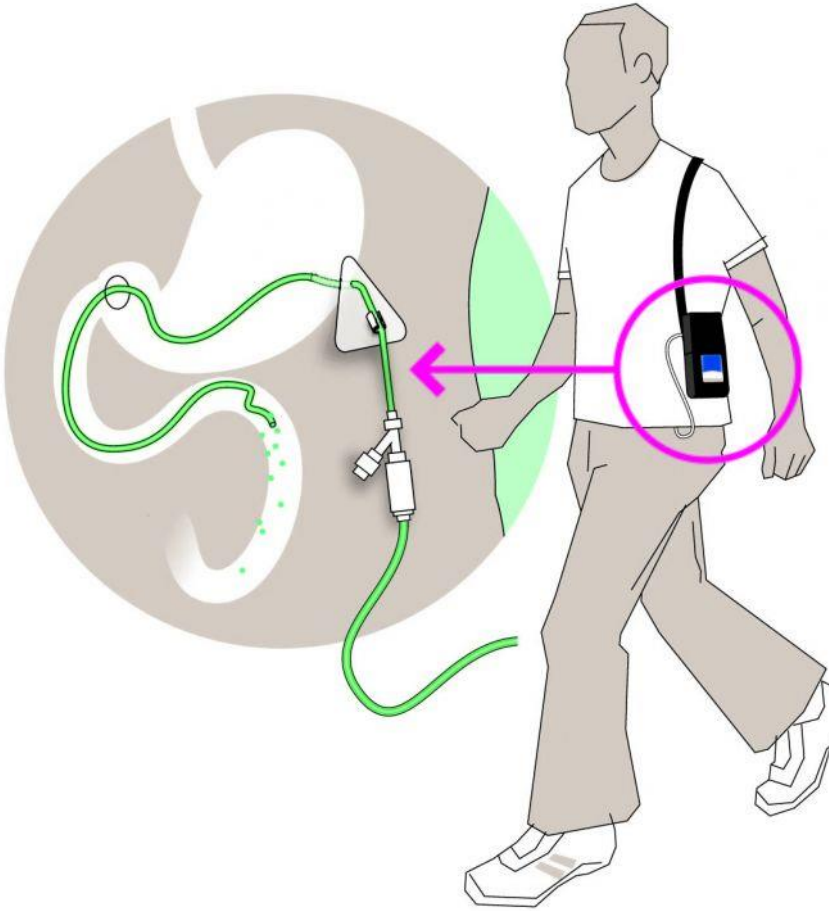
0·0004 *vs* immediate-release carbidopa-levodopa group by ANCOVA. †p<0·0001 *vs* immediate-release idopa-levodopa group by ANCOVA.

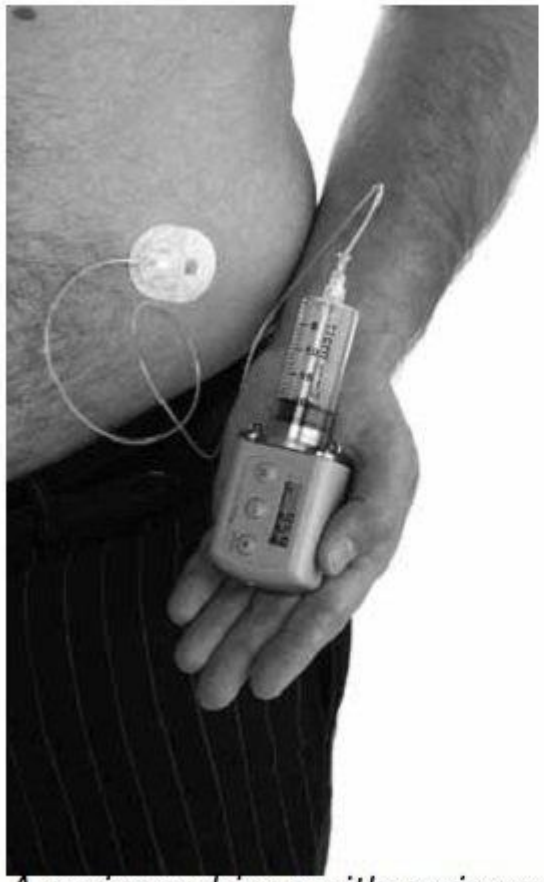
able 1: Conversion from Immediate-Release Carbidopa-Levodopa to RYTARY

Total Daily Dose of Levodopa in Immediate-Release Carbidopa-Levodopa	Recommended Starting Dosage of RYTARY	
	Total Daily Dose of Levodopa in RYTARY	RYTARY Dosing Regimen
400 mg to 549 mg	855 mg	3 capsules RYTARY 23.75 mg / 95 mg taken TID[a]
550 mg to 749 mg	1140 mg	4 capsules RYTARY 23.75 mg / 95 mg taken TID
750 mg to 949 mg	1305 mg	3 capsules RYTARY 36.25 mg / 145 mg taken TID
950 mg to 1249 mg	1755 mg	3 capsules RYTARY 48.75 mg / 195 mg taken TID
Equal to or greater than 1250 mg	2340 mg or	4 capsules RYTARY 48.75 mg / 195 mg taken TID or
	2205 mg	3 capsules RYTARY 61.25 mg / 245 mg taken TID

TID: three times a day

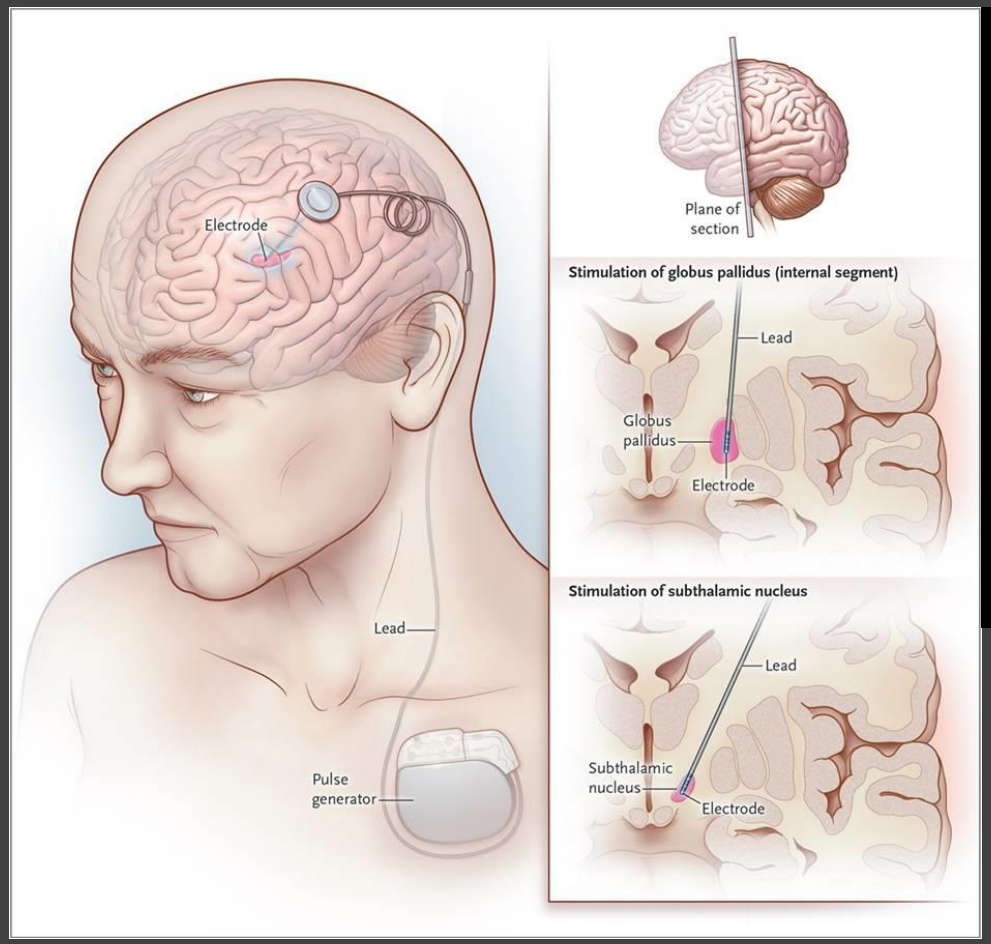
DuoDopa/Apomorphin

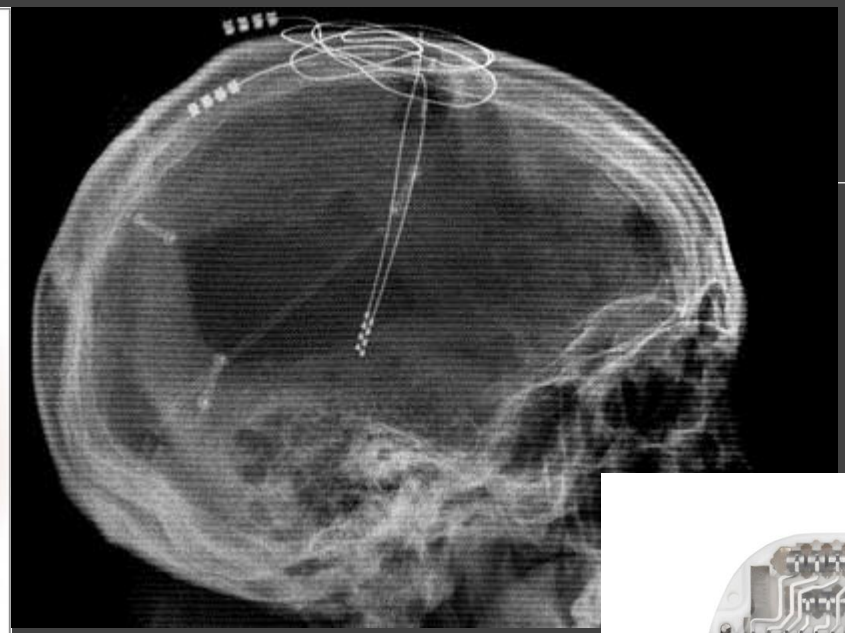


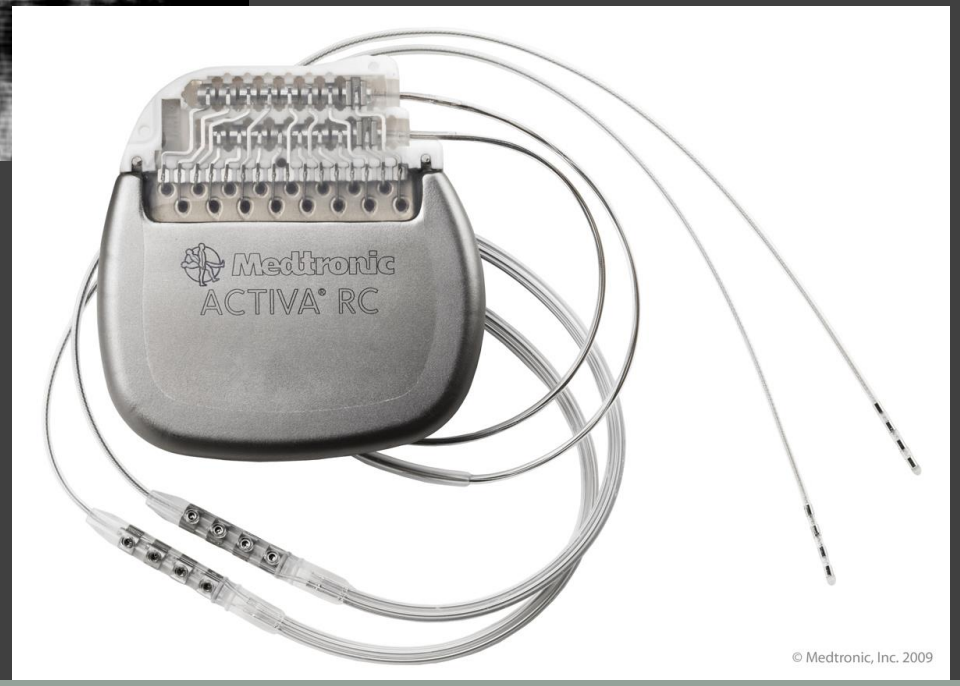


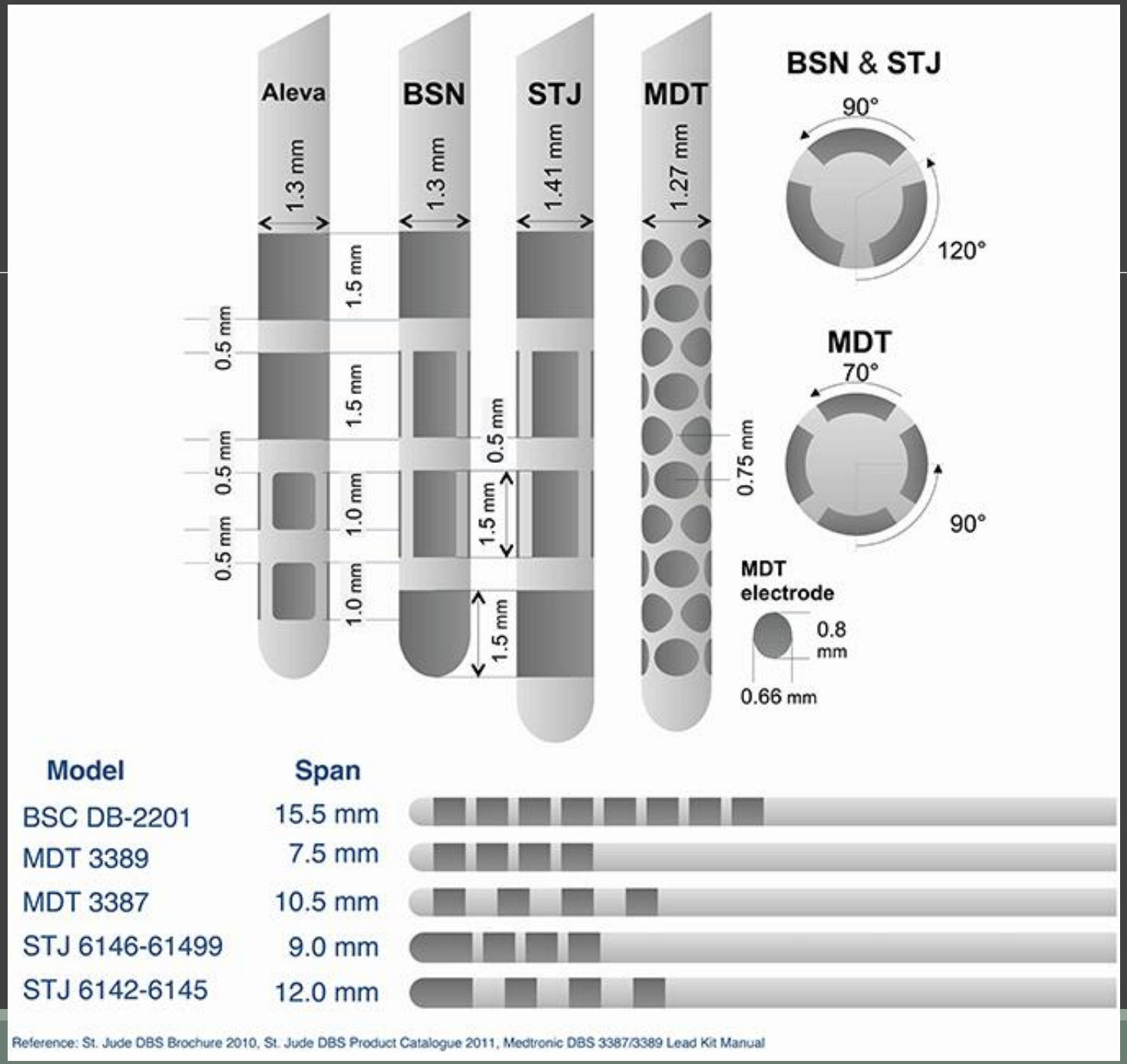
A syringe driver with syringe attached

深腦刺激術(Deep Brain Stimulation)









Model	Span
BSC DB-2201	15.5 mm
MDT 3389	7.5 mm
MDT 3387	10.5 mm
STJ 6146-61499	9.0 mm
STJ 6142-6145	12.0 mm

Reference: St. Jude DBS Brochure 2010, St. Jude DBS Product Catalogue 2011, Medtronic DBS 3387/3389 Lead Kit Manual

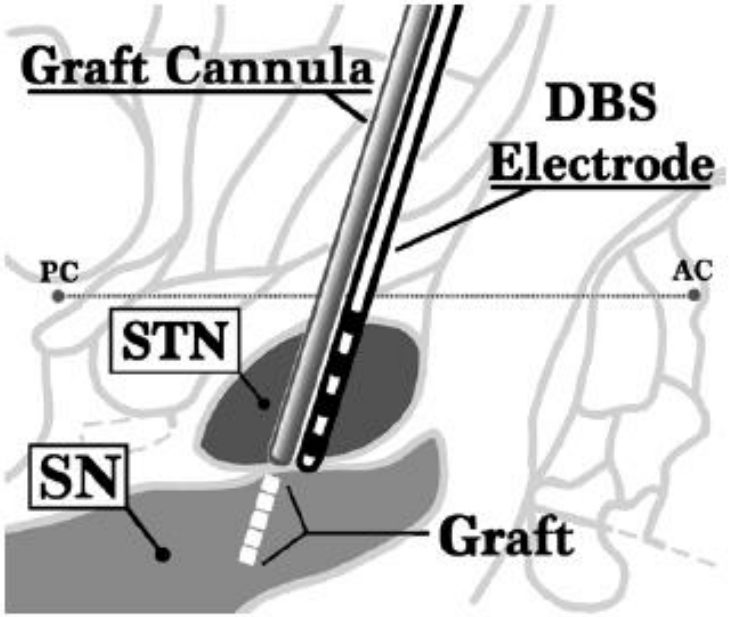


FIG. 2. Graft delivery was targeted to the substantia nigra at 1–6 mm below the base of the STN where the DBS leads were implanted. The anterior commissure–posterior commissure line is shown. AC = anterior commissure; PC = posterior commissure; SN = substantia nigra.

inner stylet (Fig. 3). The stylet was then locked in place with set screws. The guide cannula was removed, and the graft cannula was placed to target through the same bur hole used for the stimulating electrode. The graft was deployed by releasing the inferior set screw and retracting the graft cannula 5 mm. After 2 minutes, the assembly was rotated in place several times to facilitate graft detachment from the assembly. The graft cannula assembly was then removed. The dura was covered with Durepair dura regeneration matrix (Medtronic) and the bur hole was filled with HydroSet. This sequencing was chosen so that the grafting procedure would not interfere with the DBS implantation.

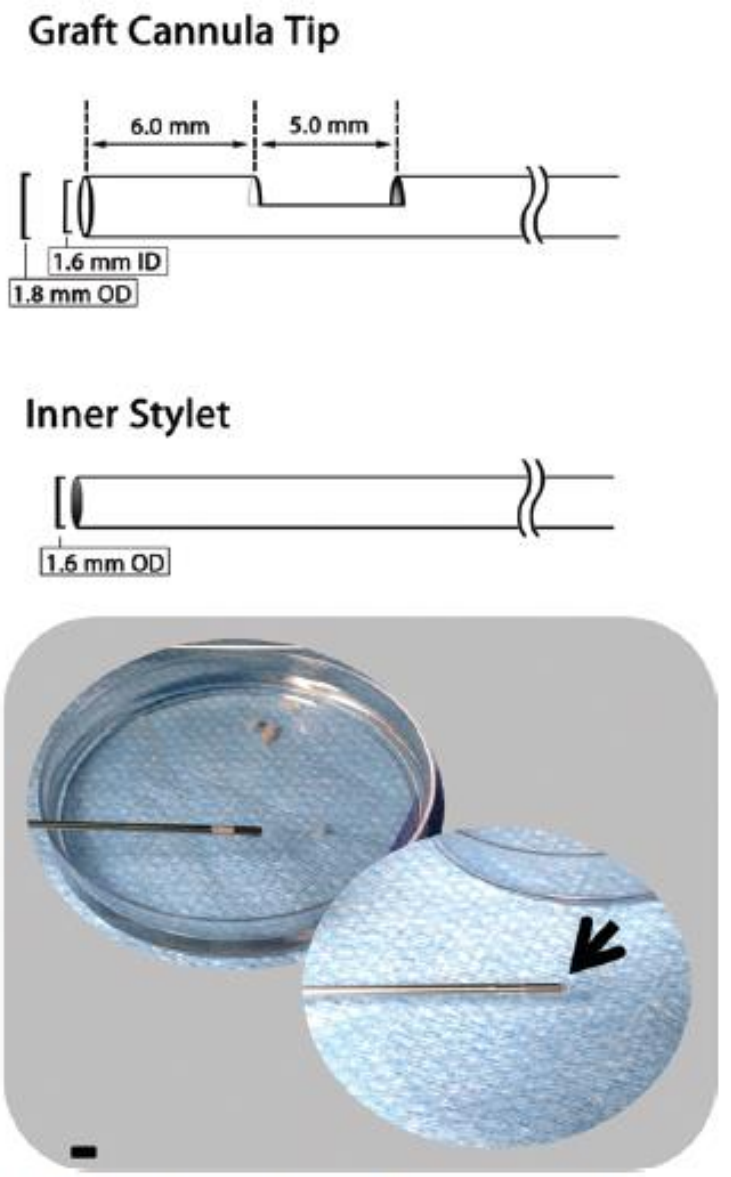


FIG. 3. **Upper:** Schematic illustration showing the graft cannula specifications. The window at the tip of the cannula is used for loading tissue

深腦刺激術(Deep Brain Stimulation)

健保署為照顧巴金森氏症病患，將自104年1月1日起將「深腦刺激術」電池納入給付，但因健保資源有限，所以在符合專家訂定的給付規定下，需同時符合下列條件：

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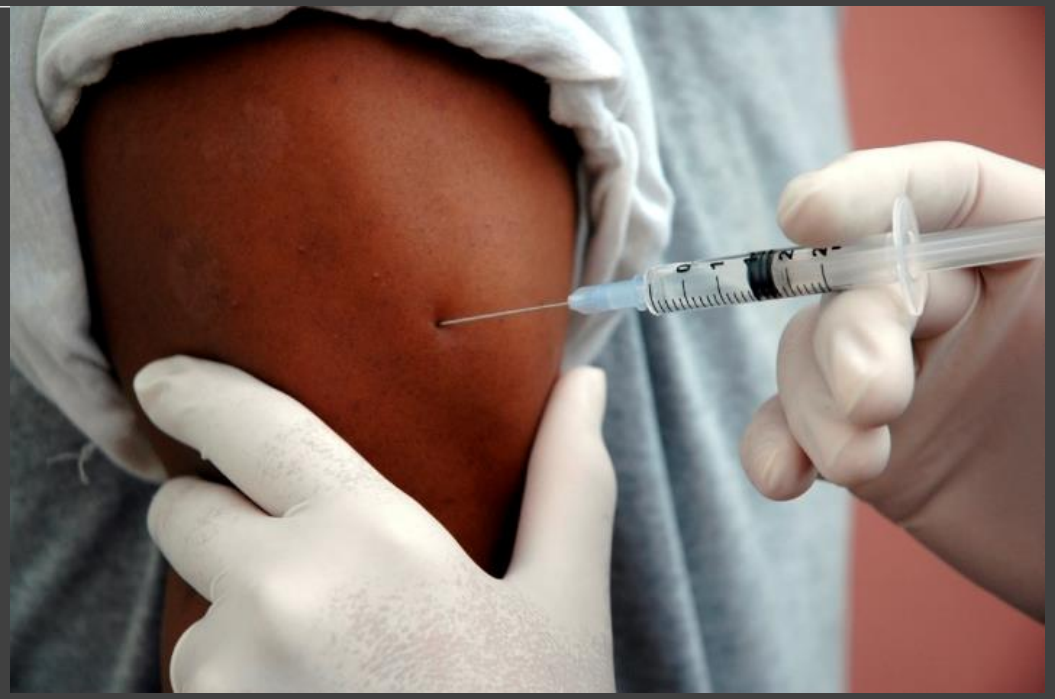
1. 屬原發性巴金森病；
2. 發病五年以上，且經醫學中心評估為藥物治療至少一年以上無反應者或因長期服藥後
2. 產生不良反應而無法繼續服藥者（註1）；
3. 病人身體其它狀況良好，必須無失智症、無其他嚴重的內外科疾病，以及無藥物無法
2. 控制之精神疾病（註2）；
4. 病人的腦部磁振造影（MRI）檢查必須正常。

每位病人以給付單側型兩個或雙側型一個為限，給付金額46萬2仟點，連同手術費用每位病人給付約48萬1仟點（註3）。

註1：病人必須接受服藥前後巴金森症狀評估及錄影
註2：失智症評估會依教育程度不同而有不同標準
註3：目前一位病人一生只給付一次電池為限

巴金森症治療疫苗(Vaccine and Monoclonal Ab Tx)



immunizations with AFFITOPE® PD01A, an active vaccine against Parkin… million grant from The Michael J. Fox Foundation for Parkinson's Research.

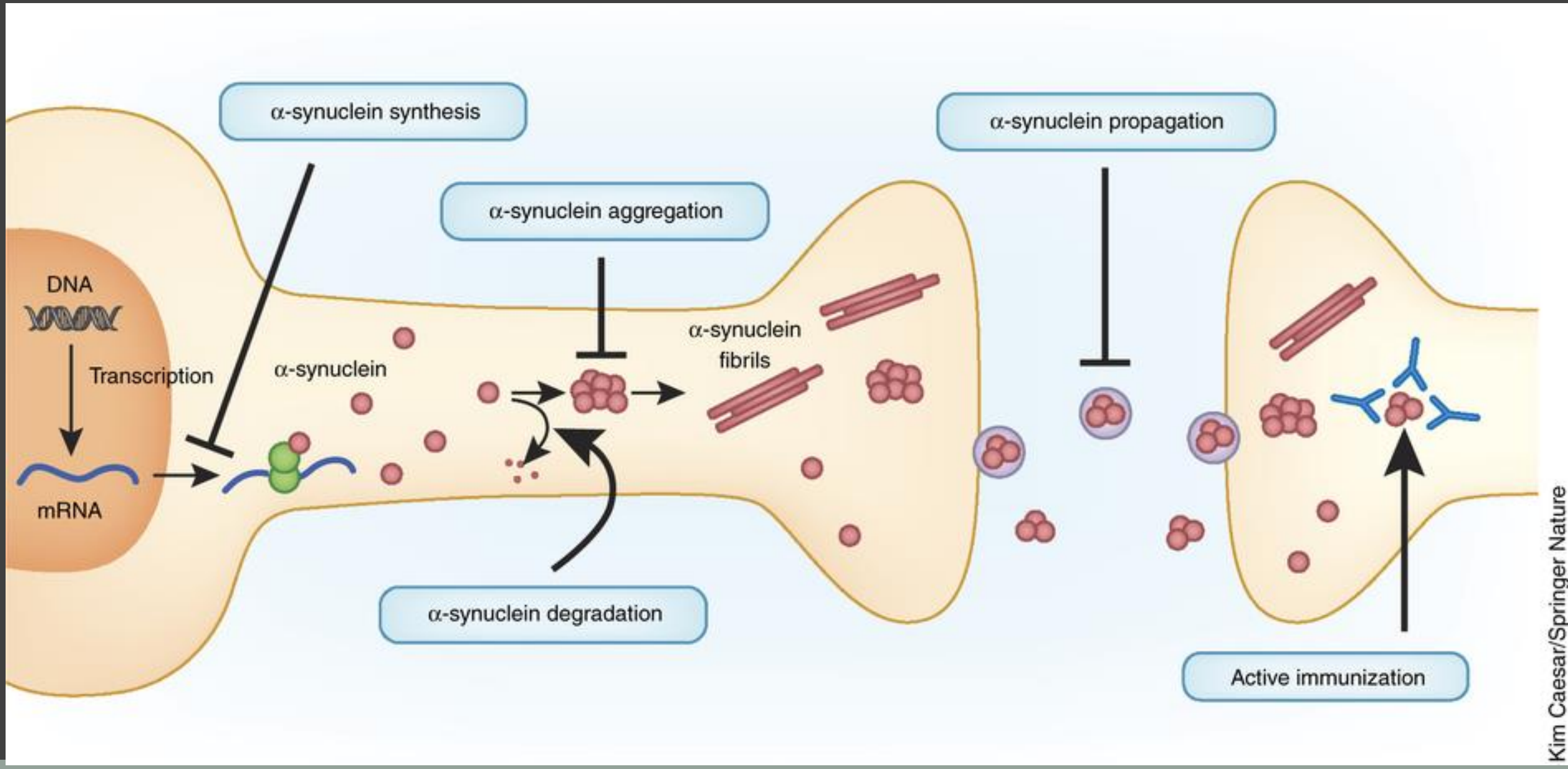
The "boost" study AFF008A was designed to assess one boost immunization with AFFITOPE® PD01A per patient with regard to safety/tolerability and immunological and clinical activity in those patients who had already received the vaccine (four "priming" vaccinations at four-week intervals) within the first-in-man clinical study AFF008. Six PD patients on best medical care, including standard symptomatic medication, served as a comparison group. In the "boost" study, two different doses of AFFITOPE® PD01A (15 µg and 75 µg) were again safe and well tolerated, meeting the primary endpoint of the trial.

Patients belonging to the low-dose group of AFF008 were randomized in two equally distributed groups receiving either 15 µg or 75 µg AFFITOPE® PD01A. The same was done with patients of the AFF008 high-dose group, in order to allow for evaluation of four different vaccination schedules.

Across all patients, no antibody concentration limiting toxicity was observed. Adverse events were similar across all five groups except injection site reactions, which only occurred in the active treatment groups, and psychiatric disorders, reported at a lower rate in the active groups. All of the 28 patients completed the study and received all planned vaccinations. Only one serious adverse event was reported, which was classified as being not related to AFFITOPE® PD01A administration.

An immune response against AFFITOPE® PD01A was seen in 19 of 22 (86%) of vaccinated patients and 12 of 19 (63%) of these responders generated aSyn-specific serum antibodies. The immune response sustained throughout the entire observation period of 24 weeks. Patients on low dose and then high dose had a clear immunological boost. This data supports that further dose and scheduling may significantly influence antibody titer/concentration and further studies need to be performed. Additionally, vaccine-induced antibodies were detectable in cerebrospinal fluid. This induction of antibodies against aSyn supports the concept of the principle of AFFiRiS' proprietary therapeutic vaccine.

Parallel laboratory experiments using recombinant aSyn protein to assess selectivity showed that AFFITOPE® PD01A-induced antibodies preferentially bind to aSyn fibrils, which are believed to be the toxic form of the protein, as compared to the monomeric form.


α-synuclein synthesis
α-synuclein aggregation
α-synuclein propagation
DNA
Transcription
mRNA
α-synuclein
α-synuclein fibrils
α-synuclein degradation
Active immunization
Kim Caesar/Springer Nature

巴金森氏症疫苗

Parkinson's Vaccine: EU-Team Launches Clinical Trial

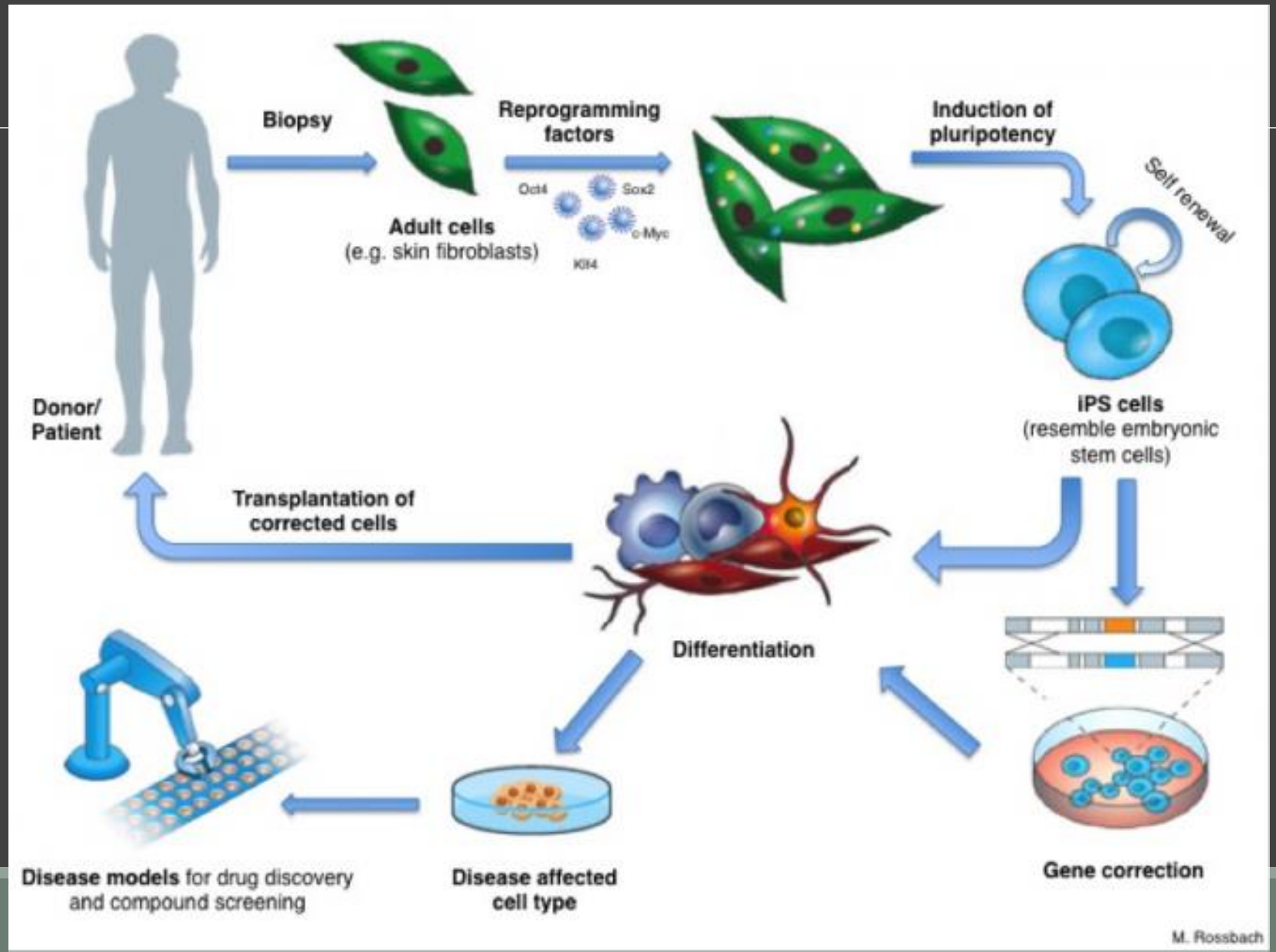
Vaccine candidate based on proprietary technology by AFFiRiS AG

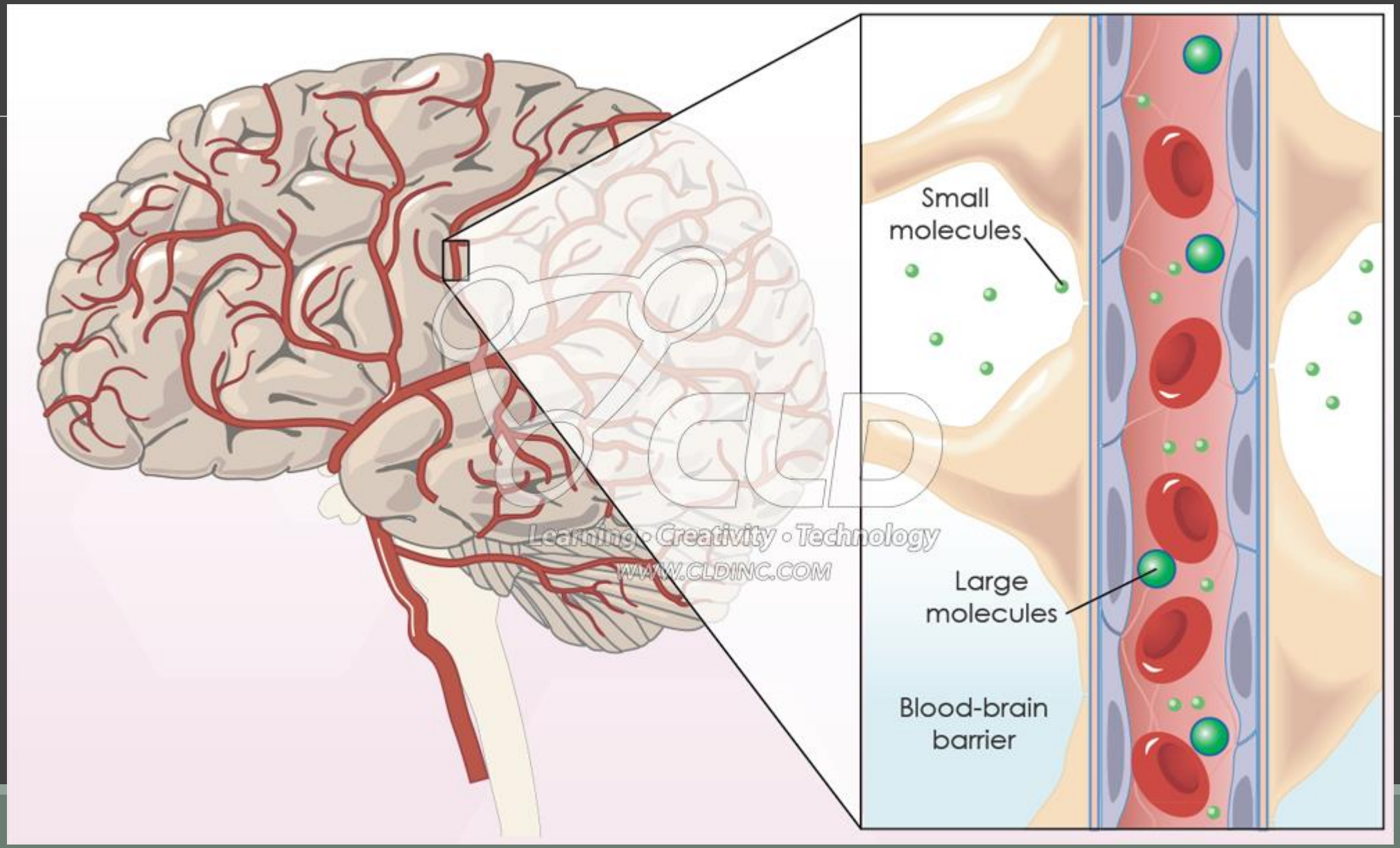
Vienna, 9 December 2014 – A novel Parkinson's vaccine will now be tested in a clinical Phase I trial in Austria by an EU-funded consortium. The vaccine was developed by the Austrian biotech company AFFiRiS AG and targets a protein called alpha-Synuclein. The protein plays a key role in the onset and progression of Parkinson's as well as multiple system atrophy (MSA), an orphan disease. This vaccine has the potential to modify disease progression, rather than only symptomatic improvements available with current treatment strategies.

The start of the Parkinson's trial follows in the wake of positive results from a similar Parkinson's vaccine trial recently conducted by AFFiRiS with support from the Michael J. Fox Foundation.

期別	目標與特色
第一期 (phase I)	●首次應用於人體的試驗 (first-in human study) ●屬於人體藥理學研究 ●受試者可以是健康受試者，或是特定疾病族群 ●受試者人數一般在30人以下 ●包括以下研究 - 藥物動力學 - 藥物效力學 - 藥品活性早期測量
第二期 (phase II)	●原理驗證(proof-of-principle) 階段 ●屬於探索性 (exploratory) 藥效研究 ●可使用各種試驗設計，包括使用對照組 ●受試對象為患有特定疾病的病人 ●受試者人數在30-70人之間 ●可以分為 IIa 或 IIb 階段 - IIa：評估新藥的短期安全性 (short-term safety) - IIb：評估療效以及劑量範圍 (dose range)
第三期 (phase III)	●必須是隨機分派控制研究 (randomized controlled study) ●目標為確認 (confirmatory)新藥是否具有療效 ●在某些情況下又可分為IIIa 和 IIIb 階段 - IIIa：主要是進行藥效評估，在submit NDA之前進行 - IIIb：主要是在submit NDA (new drug application)之後一直到正式上市之間的這段時間進行，目標主要是完成較早期研究沒有研究到的項目，例如新藥對生活品質 (QoL)的影響
第四期 (phase IV)	●新藥經過核准上市後，所進行的研究，又稱為銷售後試驗(post-marketing trial)，或是註冊後試驗 (post-registration trial) ●目標為持續評估新藥上市後的藥效和安全評估 ●另一目標為評估新藥對健康經濟學 (health economics)的影響

Stem cell therapy




Small molecules
Large molecules
Blood-brain barrier
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結語

每個醫療世代都有治療的極限，也許在我們這個世代仍沒有辦法根除巴金森症的退化，但請保持希望，隨著神經科學在巴金森症研究上的持續進步，多元的治療層面是相當有潛力的。

結語

請永遠記得:
不論是現代醫療或傳統醫療都沒有所謂仙丹妙藥，可以徹底根除腦部的退化性疾病，對巴金森症的病友們來說，規則服藥的最大目的應該是維持所需的活動度以及愉悅的心情，盡可能的回到社會、回到家庭，快樂的生活!

謝謝聆聽!!