Effects of repetitive transcranial magnetic stimulation on post-stroke patients with cognitive impairment: A systematic review and meta-analysis

Li, KP., Sun, J., Wu, CQ., et al.(2023). Behavioural Brain Research, 439, 114229.

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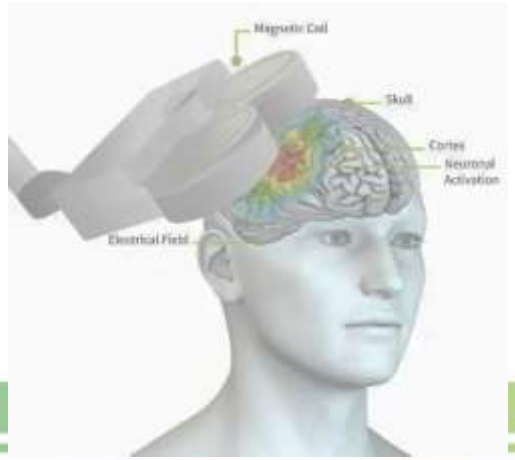
Outline

1. 重複經顱磁刺激簡介
2. Background
3. PICO
4. Critical appraisal
5. CASP 系統性文獻回顧檢核表

重複經顱磁刺激
（Repetitive Transcranial magnetic stimulation, rTMS）

- 1985年由Anthony Barker提出使用，非侵入性電刺激
- 原理利用電磁感應產生磁場，在目標大腦皮質區域產生電流，造成神經細胞去極化，隨後產生目標動作，能刺激大腦皮質及周邊神經。
- rTMS在不同的頻率組合中可以改變大腦皮質的活性及相對應功能，目前研究顯示低頻（1Hz）的重複經顱磁刺激（LF-rTMS）有抑制大腦活性的作用，高頻（>5Hz）的重複經顱磁刺激（HF-rTMS）有促進大腦活性的作用。



重複經顱磁刺激
（Repetitive Transcranial magnetic stimulation, rTMS）

- rTMS最早開始應用在治療情緒及大腦高階問題的個案身上，如憂鬱症、失眠，rTMS可以增加或是減少目標腦區的活性，進而達到大腦各區之間的平衡，研究已證實治療憂鬱症病人有顯著成效。

- 近年研究rTMS對於中風及巴金森氏症等運動能力受損的個案也有不錯的成效，利用rTMS促進或抑制大腦運動皮質的活性後，搭配傳統的運動治療訓練，可以改善中風個案的行走速度與功能、上肢活動功能、提升平衡能力。

Background

- For post-stroke patients, insufficient blood and oxygen supply to brain can contribute to the structural changes and degeneration of neural tissue.
- ↓ attention, orientation, memory & visuospatial function

J. Neurol. Sci., 359 (1) (2015), pp. 219-225

- Evidence has shown that individuals with post-stroke cognitive impairment(PSCI) account for 30–50% among stroke patients, with an incidence of dementia up to 8.2% and 34.4% in mild and severe survivors, respectively.

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臨床問題	重複經顱磁刺激是否可改善中風病人的認知能力?
問題/研究族群 **P**roblem/Patient	Patients meeting the diagnostic criteria for stroke through head computed tomography or magnetic resonance imaging, cognitive impairment confirmed by cognitive function assessment, age of 18 years or older, stroke type and stage were not restricted.
給予的措施 **I**ntervention	Repetitive Transcranial magnetic stimulation, rTMS
對照組 **C**omparison	Sham rTMS
結果 **O**utcome	•Global cognition (MoCA & MMSE) •Cognition performance •Depression •Ability of daily living

蒙特利爾認知評估(Montreal Cognitive Assessment ; MoCA)	簡短智能測驗 (Mini-Mental State Examination; MMSE)
用來快速篩選輕度認知障礙個案的量表。它量度不同領域的認知功能：專注力與集中力、執行功能、記憶力、語言能力、視覺空間建構、抽象概念、計算與定位。完成整個量表的時間約為十分鐘。 總分為30分。英文原版的測試結果顯示取得26分或以上為正常。	針對認知功能所設計的評估工具，總共十一個問題，包括時間與地方定向能力、注意力與算術能力、立即記憶與短期記憶、語言 (包括讀、寫、命名、理解、與操作) 能力、視覺空間能力等認知功能，施測只需 5 到 10 分鐘。最高得分 30 分，得分越高，表示能力越好。 台灣研究曾發現因教育程度不同分界值也不同，18分以上為正常。

CRITICAL APPRAISAL

- **Methods**
- **Results**
- **Discussion**

Methods

- Search words included (“ Stroke ” , “ Cerebrovascular Accidents ” , “ CVA ” , “ Cere-brovascular Apoplexy ” , “ Brain Vascular Accident ” , “ Cerebrovascular Stroke ” , “ Apoplexy ” , “ Cerebral Stroke ” , “ Acute Stroke ” , “ Acute Cere-brovascular Accident ”) AND (“ Transcranial Magnetic Stimulation ” , “ rTMS ”) AND (“ Cognitive Dysfunction ” , “ Cognitive Impairment ” , “ Mild Neurocognitive Disorder ” , “ Cognitive Decline ”).
- Records published before the end of February on 2022 on rTMS and PSCI were retrieved from PubMed, Cochrane Library, EBSCO, Embase and Scopus.
- Two researchers independently evaluated the quality of included literature in accordance with Cochrane Systematic Review Manual.

Methods

Inclusion criteria

(1) Research type: RCT, Chinese or English;

(2) Study population: patients meeting the diagnostic criteria for stroke through head CT or MRI, cognitive impairment confirmed by cognitive function assessment , age of 18 years or older, stroke type and stage were not restricted.

Exclusion criteria

(1) Duplicate published articles;

(2) Papers without access to full text or raw data;

(3) Studies with a high bias (for example, improper study design, incongruent metasomatism).

Results

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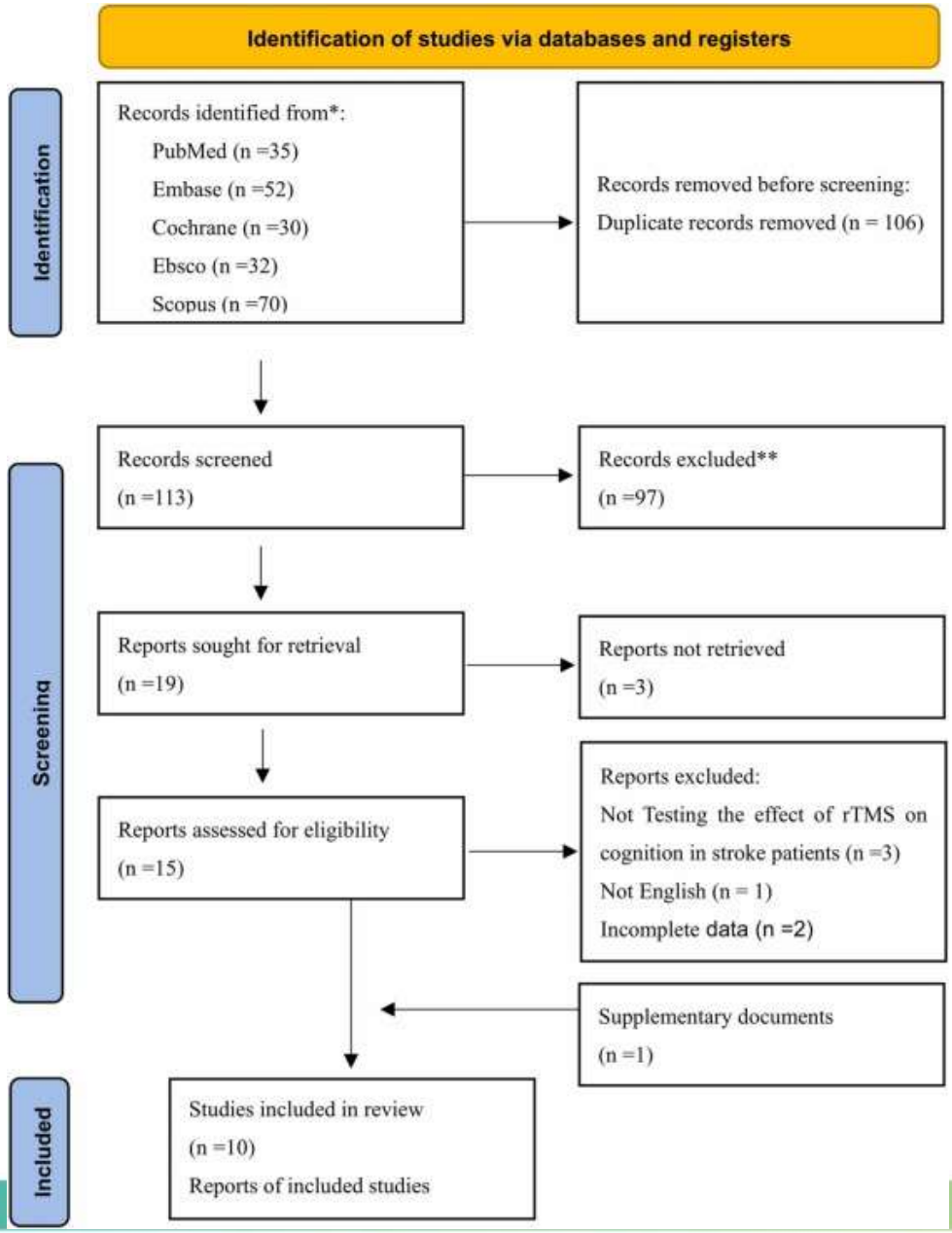

Identification of studies via databases and registers
Identification
Records identified from*:
PubMed (n =35)
Embase (n =52)
Cochrane (n =30)
Ebsco (n =32)
Scopus (n =70)
Records removed before screening:
Duplicate records removed (n = 106)
Screening
Records screened
(n =113)
Records excluded**
(n =97)
Reports sought for retrieval
(n =19)
Reports not retrieved
(n =3)
Reports assessed for eligibility
(n =15)
Reports excluded:
Not Testing the effect of rTMS on cognition in stroke patients (n =3)
Not English (n = 1)
Incomplete data (n =2)
Supplementary documents
(n =1)
Included
Studies included in review
(n =10)
Reports of included studies

Table 1
The basic characteristics of the included research.

rTMS studies	Age (yrs)	Male/ Female	Education (yrs)	Disease course (days)	Ischemic/ Hemorrhage	Age (yrs)	Male/ Female	Education (yrs)	Disease course (days)	Ischemic/ Hemorrhage
	Active					Sham				
Po-Yi Tsai (2020) [25]	57.45 ± 12.3	9/2	14 ± 2.8	33.27 ± 26.4	3/8	56.23 ± 12	13/2	13.64 ± 1.9	38 ± 7.9	10/5
Felipe Fregni (2006) [26]	57.70 ± 11.27	8/2	–	105.6 ± 87.9	–	52.60 ± 12.56	3/2	–	119.1 ± 79.2	–
Kim BR (2010) [27]	53.5 ± 16.9	4/2	–	241.2 ± 42.5	4/2	66.8 ± 17.2	4/2	–	69.7 ± 39.0	5/1
	68.3 ± 7.4	2/4	–	404.4 ± 71.7	5/1					
Haitao Lu (2015) [31]	42.5 ± 12.3	12/7	12.8 ± 3.8	67 (30 , 365)	8/11	47.3 ± 11.8	13/8	11.5 ± 4.5	56 (30 , 296)	10/11
Yuanwen Liu (2017) [32]	65.33 ± 7.05	11/7	7.56 ± 3.81	253.2 ± 53.7	13/5	62.61 ± 9.98	9/9	9.50 ± 4.88	279.9 ± 49.2	12/6
Mingyu Yin (2018) [33]	58.58 ± 11.98	11/1	9.54 ± 3.24	59.83 ± 30.59	10/2	60.15 ± 10.29	12/1	8.92 ± 3.57	56.15 ± 23.74	10/3
Yamei Li (2020) [34]	65.47 ± 3.68	7/8	19.13 ± 7.95	22.73 ± 8.05	–	64.53 ± 4.72	9/6	9.07 ± 2.63	9.20 ± 2.31	–
Yuanwen Liu (2020) [35]	58.55 ± 6.24	10/19	9.76 ± 2.80	263.7 ± 55.2	20/9	57.69 ± 7.25	16/13	8.55 ± 3.32	258.6 ± 55.2	15/14
Mingyu Yin (2020) [36]	56.69 ± 12.92	14/2	10.03 ± 4.15	52 (38.25 , 98.75)	11/5	58.17 ± 11.27	16/2	9.33 ± 3.87	55 (39.75 , 94.75)	12/6
Hong , Li (2021) [37]	61.79 ± 5.51	21/12	10.21 ± 1.60	28.64 ± 12.60	22/11	59.47 ± 6.75	19/13	10.47 ± 1.92	27.78 ± 11.01	18/14

rTMS (n=175)	Sham (n=172)
42.5 ~ 68.3 y/o	47.3 ~ 66.8 y/o

*male : 223 (64.2%)
*infarction stroke : 188 (62.3%)
*disease course : 9 to 404 days

Results

Table 2
rTMS parameters of included records.

Study	Stimulation Position	Intensity	Total pulse	Duration
Hong，Li (2021)	the contralateral DLPFC	1hz	1000 pulse	5 days per week for 4 weeks (total 20 times)
Po-Yi Tsai (2020)	the left DLPFC	5hz	600 pulse	5 days per week for 2 weeks (total 10 times)
Mingyu Yin (2020)	the left DLPFC	10hz	2000 pulse	5 days per week for 4 weeks (total 20 times)
Yuanwen Liu (2020)	the left DLPFC	10hz	700 pulse	5 days per week for 4 weeks (total 20 times)
Yamei Li (2020)	the left DLPFC	5hz	2000 pulse	5 days per week for 3weeks (total 15 times)
Mingyu Yin (2018)	the left DLPFC	10hz	2000 pulse	5 days per week for 4 weeks (total 20 times)
Yuanwen Liu (2017)	the left DLPFC	10hz	700 pulse	5 days per week for 4 weeks (total 20 times)
Haitao Lu (2015)	the right DLPFC	1hz	600 pulse	5 days per week for 4 weeks (total 20 times)
Kim BR (2010)	the left DLPFC	10hz	450 pulse	5 days per week for 2 weeks (total 10 times)
	the left DLPFC	1hz	900 pulse	5 days per week for 2 weeks (total 10 times)
Felipe Fregni (2006)	the FDI cortical area	5hz	1200 pulse	5 days per week for 1 weeks (total 5 times)

*DLPFC: dorsolateral prefrontal cortex

*FDI: first dorsal interosseous

Results

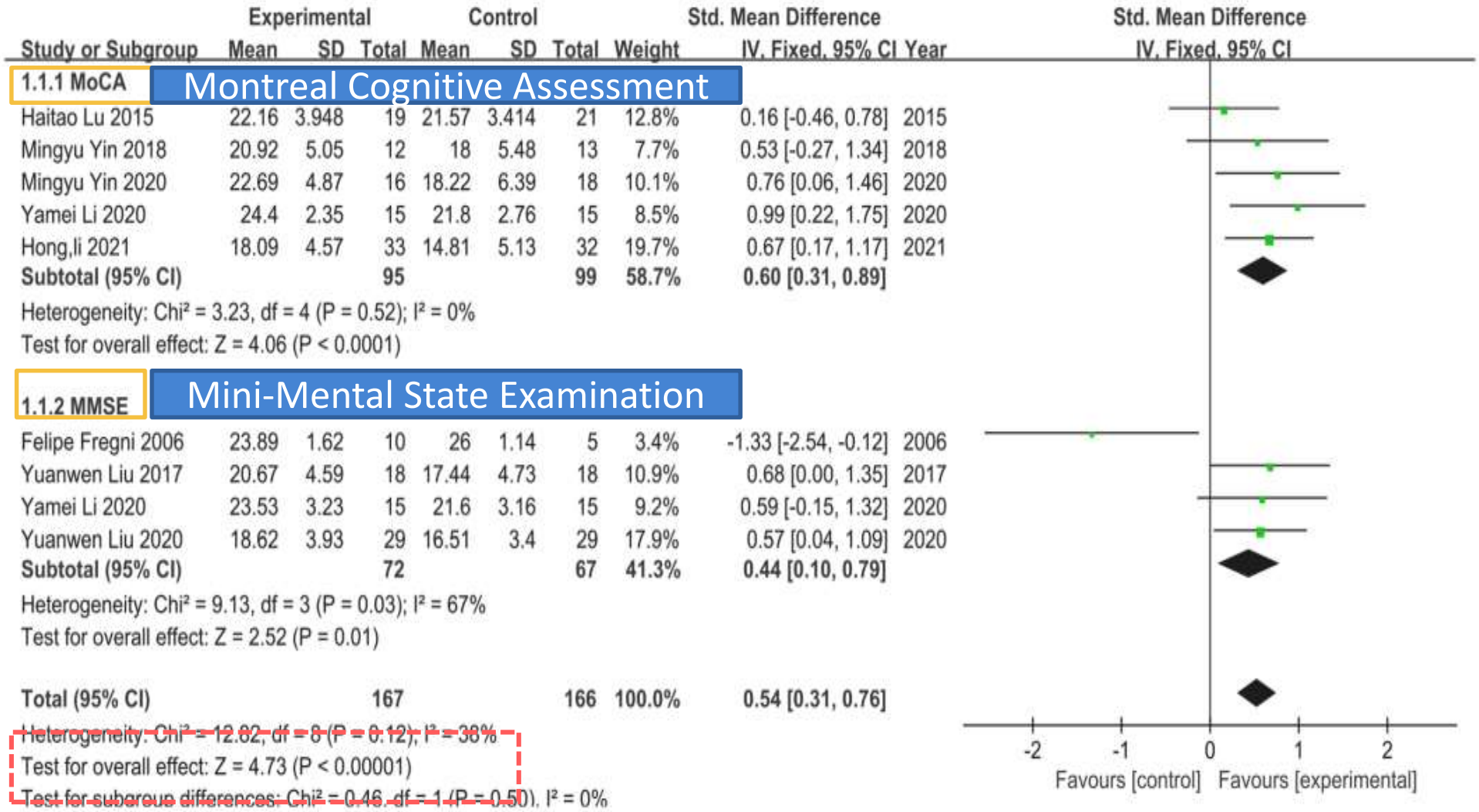
Table 3

Results of Methodological quality evaluation.

Author /Year	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Recommendation
Hong , Li 2021	+	?	+	+	-	+	?	-
Po-Yi Tsai 2020	+	+	+	+	-	+	?	?
Mingyu Yin 2020	+	?	+	+	-	+	?	-
Yuanwen Liu 2020	+	+	+	+	-	+	?	?
Yamei Li 2020	+	?	+	+	+	+	?	+
Mingyu Yin 2018	+	?	+	+	+	+	?	+
Yuanwen Liu 2017	+	?	+	+	+	+	?	+
Haitao Lu 2015	+	?	+	+	+	+	?	+
Kim BR 2010	+	?	+	+	+	+	?	+
Felipe Fregni 2006	+	?	+	+	+	+	?	+

Note: Item 1: randomenzation;Item2: allocation concealment; Item 3: blindness of participants and personnel ; Item 4: blindness of outcome evaluator; Item 5: outcomes measured reliably; Item 6: selective reporting; Item 7: Other bias. + : Low Risk;?: Unclear Risk; -: High Risk

Effects of rTMS on global cognition

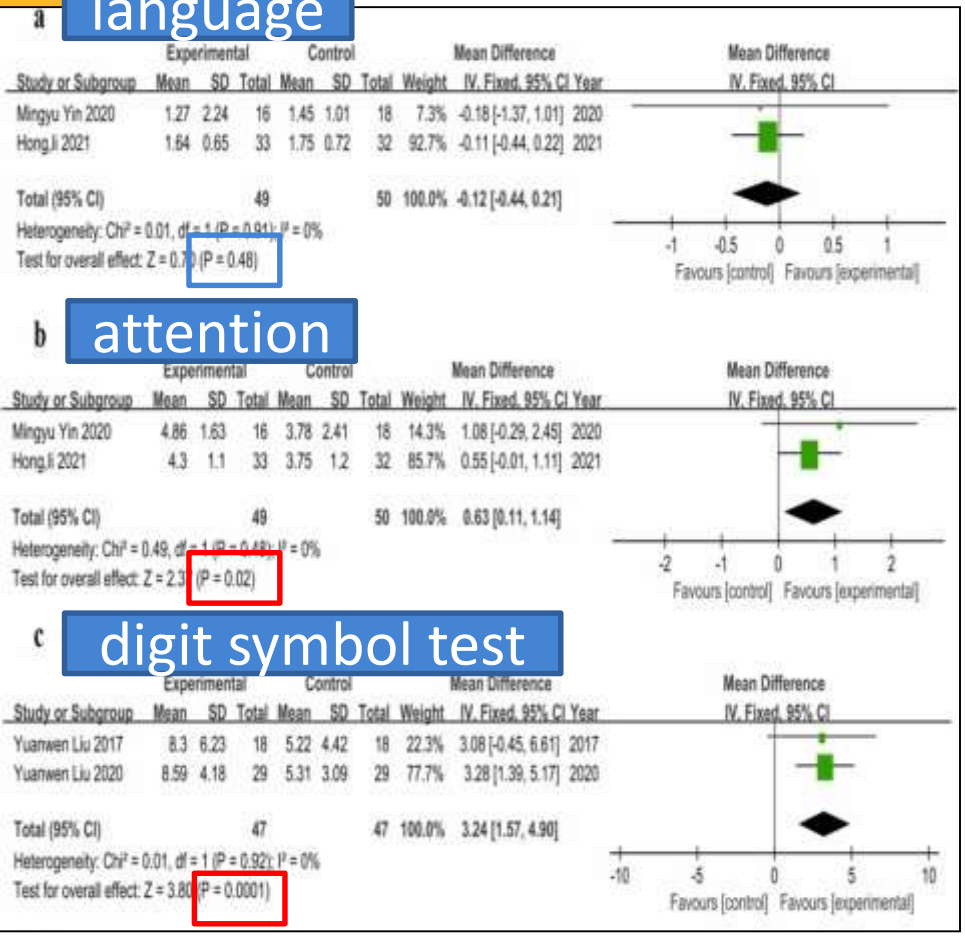


Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
1.1.1 MoCA (Montreal Cognitive Assessment)									
Haitao Lu 2015	22.16	3.948	19	21.57	3.414	21	12.8%	0.16 [-0.46, 0.78]	2015
Mingyu Yin 2018	20.92	5.05	12	18	5.48	13	7.7%	0.53 [-0.27, 1.34]	2018
Mingyu Yin 2020	22.69	4.87	16	18.22	6.39	18	10.1%	0.76 [0.06, 1.46]	2020
Yamei Li 2020	24.4	2.35	15	21.8	2.76	15	8.5%	0.99 [0.22, 1.75]	2020
Hong,li 2021	18.09	4.57	33	14.81	5.13	32	19.7%	0.67 [0.17, 1.17]	2021
Subtotal (95% CI)			**95**			**99**	**58.7%**	**0.60 [0.31, 0.89]**	
Heterogeneity: Chi² = 3.23, df = 4 (P = 0.52); I² = 0%									
Test for overall effect: Z = 4.06 (P < 0.0001)									
1.1.2 MMSE (Mini-Mental State Examination)									
Felipe Fregni 2006	23.89	1.62	10	26	1.14	5	3.4%	-1.33 [-2.54, -0.12]	2006
Yuanwen Liu 2017	20.67	4.59	18	17.44	4.73	18	10.9%	0.68 [0.00, 1.35]	2017
Yamei Li 2020	23.53	3.23	15	21.6	3.16	15	9.2%	0.59 [-0.15, 1.32]	2020
Yuanwen Liu 2020	18.62	3.93	29	16.51	3.4	29	17.9%	0.57 [0.04, 1.09]	2020
Subtotal (95% CI)			**72**			**67**	**41.3%**	**0.44 [0.10, 0.79]**	
Heterogeneity: Chi² = 9.13, df = 3 (P = 0.03); I² = 67%									
Test for overall effect: Z = 2.52 (P = 0.01)									
Total (95% CI)			**167**			**166**	**100.0%**	**0.54 [0.31, 0.76]**	
Heterogeneity: Chi² = 12.82, df = 8 (P = 0.12); I² = 38%									
Test for overall effect: Z = 4.73 (P < 0.00001)									
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%									

Fig. 2. Forest plot of general cognitive function assessed by MMSE or MoCA.

Effects of rTMS on other cognition performance

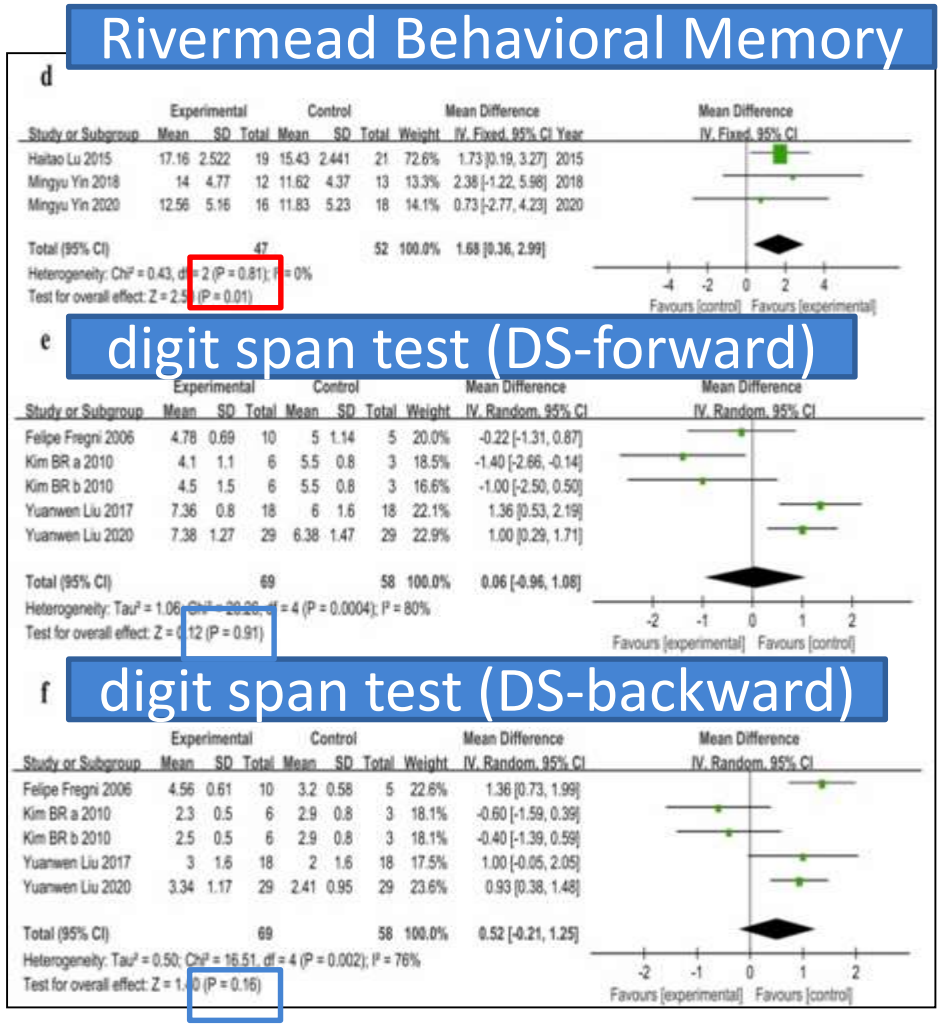
language



attention

digit symbol test

Rivermead Behavioral Memory

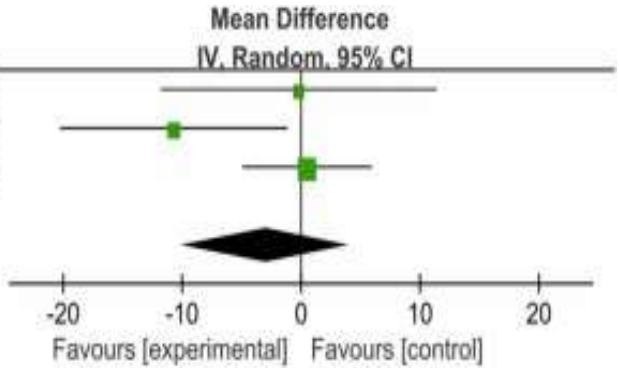


Effects of rTMS on depression

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Kim BR a 2010	13.8	8.5	6	14	8.3	3	23.6%	-0.20 [-11.80, 11.40]	2010
Kim BR b 2010	3.3	2.3	6	14	8.3	3	29.6%	-10.70 [-20.27, -1.13]	2010
PY Tsai 2020	8.3	6.5	11	7.8	7.6	15	46.8%	0.50 [-4.94, 5.94]	2020
Total (95% CI)			23			21	100.0%	**-2.98 [-10.05, 4.09]**	

Heterogeneity: $Tau^2 = 20.11$; $Chi^2 = 4.08$, df = 2 (P = 0.13); $I^2 = 51\%$

Test for overall effect: Z = 0.83 (P = 0.41)

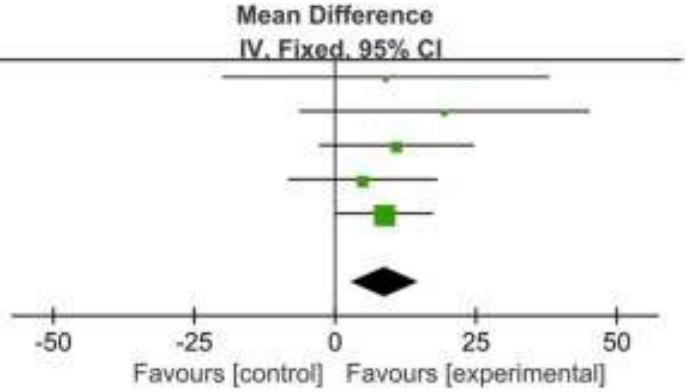


Effects of rTMS on the ability of daily living

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Kim BR a 2010	69.8	24.3	6	60.8	19.1	3	4.4%	9.00 [-20.07, 38.07]	2010
Kim BR b 2010	80.2	17.5	6	60.8	19.1	3	5.6%	19.40 [-6.35, 45.15]	2010
Mingyu Yin 2018	61.92	18.46	12	51	16.52	13	19.4%	10.92 [-2.85, 24.69]	2018
Mingyu Yin 2020	61.81	17.67	16	56.89	21.73	18	21.0%	4.92 [-8.34, 18.18]	2020
Hong,li 2021	62.21	16.58	33	53.41	18.71	32	49.7%	8.80 [0.20, 17.40]	2021
Total (95% CI)			73			69	100.0%	**9.00 [2.93, 15.06]**	

Heterogeneity: $Chi^2 = 1.07$, df = 4 (P = 0.90); $I^2 = 0\%$

Test for overall effect: Z = 2.91 (P = 0.004)



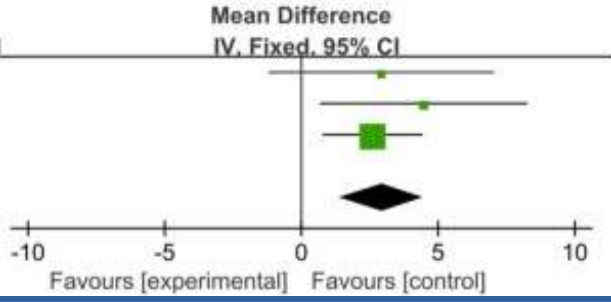
Subgroup analysis of global cognition

a high frequency rTMS on MoCA score

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mingyu Yin 2018	20.92	5.05	12	18	5.48	13	13.8%	2.92 [-1.21, 7.05]
Mingyu Yin 2020	22.69	4.87	16	18.22	6.39	18	16.3%	4.47 [0.67, 8.27]
Yamei Li 2020	24.4	2.35	15	21.8	2.76	15	69.9%	2.60 [0.77, 4.43]
Total (95% CI)			**43**			**46**	**100.0%**	**2.95 [1.42, 4.48]**

Heterogeneity: Chi² = 0.76, df = 2 (P = 0.69); I² = 0%

Test for overall effect: Z = 3.77 (P = 0.0002)

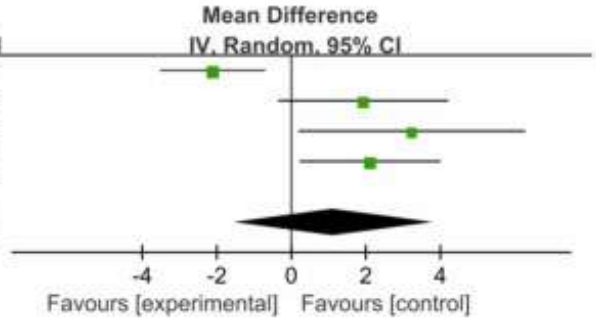


b high frequency rTMS on MMSE score

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Felipe Fregni 2006	23.89	1.62	10	26	1.14	5	27.7%	-2.11 [-3.53, -0.69]
Yamei Li 2020	23.53	3.23	15	21.6	3.16	15	24.6%	1.93 [-0.36, 4.22]
Yuanwen Liu 2017	20.67	4.59	18	17.44	4.73	18	21.6%	3.23 [0.19, 6.27]
Yuanwen Liu 2020	18.62	3.93	29	16.51	3.4	29	26.1%	2.11 [0.22, 4.00]
Total (95% CI)			**72**			**67**	**100.0%**	**1.14 [-1.52, 3.80]**

Heterogeneity: Tau² = 6.12; Chi² = 20.13, df = 3 (P = 0.0002); I² = 85%

Test for overall effect: Z = 0.84 (P = 0.40)

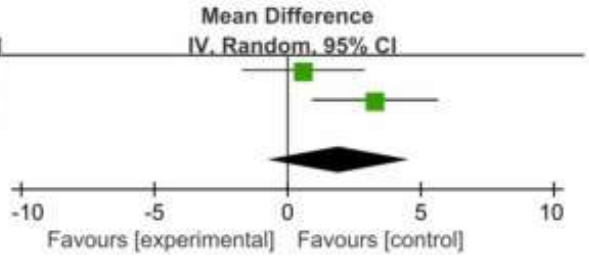


c low frequency rTMS on MoCA score

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Haitao Lu 2015	22.16	3.948	19	21.57	3.414	21	50.6%	0.59 [-1.71, 2.89]
Hong,li 2021	18.09	4.57	33	14.81	5.13	32	49.4%	3.28 [0.92, 5.64]
Total (95% CI)			**52**			**53**	**100.0%**	**1.92 [-0.72, 4.56]**

Heterogeneity: Tau² = 2.20; Chi² = 2.56, df = 1 (P = 0.11); I² = 61%

Test for overall effect: Z = 1.43 (P = 0.15)



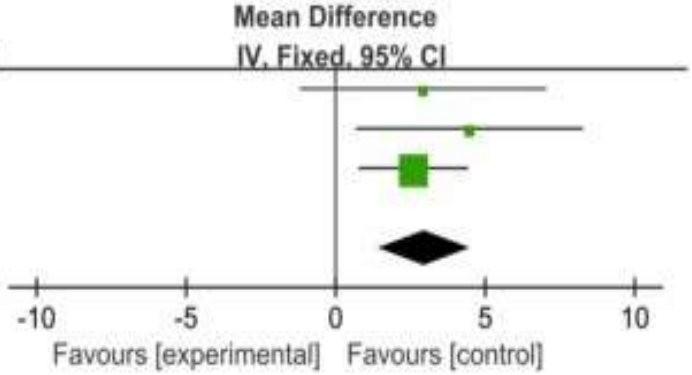
Subgroup analysis of global cognition

a MoCA score by rTMS on the left dorsolateral prefrontal cortex

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Mingyu Yin 2018	20.92	5.05	12	18	5.48	13	13.8%	2.92 [-1.21, 7.05]
Mingyu Yin 2020	22.69	4.87	16	18.22	6.39	18	16.3%	4.47 [0.67, 8.27]
Yamei Li 2020	24.4	2.35	15	21.8	2.76	15	69.9%	2.60 [0.77, 4.43]
Total (95% CI)			**43**			**46**	**100.0%**	**2.95 [1.42, 4.48]**

Heterogeneity: Chi² = 0.76, df = 2 (P = 0.69); I² = 0%

Test for overall effect: Z = 3.77 (P = 0.0002)

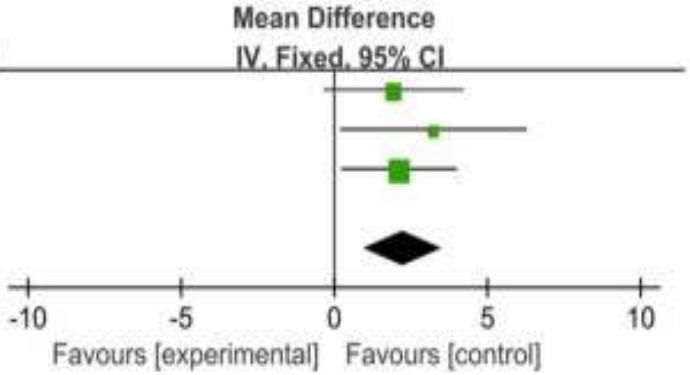


b MMSE score by rTMS on the left dorsolateral prefrontal cortex

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Yamei Li 2020	23.53	3.23	15	21.6	3.16	15	33.0%	1.93 [-0.36, 4.22]
Yuanwen Liu 2017	20.67	4.59	18	17.44	4.73	18	18.6%	3.23 [0.19, 6.27]
Yuanwen Liu 2020	18.62	3.93	29	16.51	3.4	29	48.3%	2.11 [0.22, 4.00]
Total (95% CI)			**62**			**62**	**100.0%**	**2.26 [0.94, 3.57]**

Heterogeneity: Chi² = 0.49, df = 2 (P = 0.78); I² = 0%

Test for overall effect: Z = 3.37 (P = 0.0008)



Discussion

- The present study showed that rTMS contributed to improvements of **general cognitive performance** and **ability of daily living** in post-stroke patients.
- MoCA was significantly improved by **high frequency rTMS**, while both MoCA and MMSE were significantly improved targeting on **left dorsolateral prefrontal cortex**.

Discussion

- The results showed that rTMS could significantly improve the score of **MoCA**, similar to the conclusion of Zhao et al. *Oncotarget, 8 (20) (2017), pp. 33864-33871*
- The increased score of **MMSE** by rTMS was significant but the effect is **weaker than MoCA**, which might be attributed to **simplicity** of this scale.
- Since MMSE lacks a test for **executive function**, **MoCA**, which is closely related to MMSE score, may be more suitable for **PSCI screening and early diagnosis**.
- A study showed that **MoCA** was more sensitive than MMSE in the evaluation of cognitive function decline at **3 months after first-episode stroke**.

Age Ageing, 42 (1) (2013), pp. 113-116

Discussion

- The results showed that **high frequency rTMS** can effectively improve the cognitive function in PSCI patients, which is consistent with the conclusion of Wang et al.'s study. *J. Mol. Neurosci., 41 (1) (2010), pp. 145-155*
- High-frequency rTMS **promotes local metabolic** levels in the brain, excites the cerebral cortex, increases cerebral blood flow, reduces apoptosis, and enhances connections between regions in the brain to improve cognitive function.

J. Psychiatry Neurosci., 45 (4) (2020), pp. 262-270

Discussion

- rTMS can improved cognitive function in PSCI patients, probably because it acts on the **dorsolateral frontal area**, which is associated with cognitive, emotional, pain, and behavioral management, and promotes blood flow and metabolism in the frontal area, which may improve cognitive function. *Front. Neurol., 11 (2020), p. 977*

Discussion

- **Limitation**

1. There may be **heterogeneity** due to the differences in inclusion criteria, follow-up period, frequency intensity, disease severity and assessment scales.
2. There may be **differences in the population characteristics** of all participants as well as in the lesions that may influence the results.
3. Because the included RCTs focused on the **immediate effect**, future studies are needed to evaluate the long-term effectiveness of rTMS on cognition in post-stroke individuals.

CASP系統性文獻回顧檢核表

(A)研究結果可信嗎?

(B)研究結果為何?

(C)研究結果對於當地病人有幫助嗎?

CASP
Critical Appraisal Skills Programme

(A)研究結果可信嗎?

1. 此篇系統性文獻回顧是否問了一個清楚、明確的問題?

問題/研究族群 **P**roblem/Patient	Patients meeting the diagnostic criteria for stroke through head computed tomography or magnetic resonance imaging, cognitive impairment confirmed by cognitive function assessment, age of 18 years or older, stroke type and stage were not restricted.
給予的措施 **I**ntervention	Repetitive Transcranial magnetic stimulation, rTMS
對照組 **C**omparison	Sham rTMS
結果 **O**utcome	•Global cognition •Cognition performance •Depression •Ability of daily living

✓	**P**opulation studied
✓	**I**ntervention given
✓	**C**omparator chosen
✓	**O**utcomes measured

是	V
不明確	
否	

(A)研究結果可信嗎?

2. 作者是否尋找適當研究型態的文獻?

2.2. Studies selection

Inclusion criteria: (1) research type: randomized controlled trial (RCT), Chinese or English; (2) study population: patients meeting the diagnostic criteria for stroke through head computed tomography or magnetic resonance imaging, cognitive impairment confirmed by cognitive function assessment [13], age of 18 years or older, stroke type and stage were not restricted. Exclusion criteria: (1) duplicate published articles; (2) papers without access to full text or raw data; (3) studies with a high bias (for example, improper study design, incongruent metasomatism). The relevant literatures retrieved from the above databases were exported to the bibliography, and then imported to EndNote to remove duplicates. Literatures whose titles and abstracts matched the inclusion were initially screened out and were further evaluated by reading of the full text. Literatures that failed to meet the criteria were excluded.

評讀的面向	
✓	有提及系統性文獻回顧的問題
✓	有適當的研究設計 (RCT)

是	V
不明確	
否	

(A)研究結果可信嗎?

3. 你認為所有重要且相關的研究都被納入?

tion number 202250078). Records published before the end of February on 2022 on rTMS and PSCI were retrieved from PubMed, Cochrane Library, EBSCO, Embase and Scopus. Eligible articles were searched using keywords and entry terms, and supplemented by manual search. Search words included ("Stroke", "Cerebrovascular Accidents", "CVA", "Cerebrovascular Apoplexy", "Brain Vascular Accident", "Cerebrovascular Stroke", "Apoplexy", "Cerebral Stroke", "Acute Stroke", "Acute Cerebrovascular Accident") AND ("Transcranial Magnetic Stimulation", "rTMS") AND ("Cognitive Dysfunction", "Cognitive Impairment", "Mild Neurocognitive Disorder", "Cognitive Decline").

評讀的面向	
✓	使用資料庫 (PubMed, EMBASE, CINAHL, CKNI, ProQuest, PEDro, CENTRAL, Scopus and Web of Science
✓	是否從參考資料清單中再進行搜尋
	與專家進行個別聯繫
✓	除了已發表的研究文獻，也搜尋未發表的研究文獻
✓	搜尋非英文的研究文獻
✓	出版日期無受限

是	V
不明確	
否	

(A)研究結果可信嗎?

4.系統性文獻回顧的作者是否評估所納入研究文獻的品質?

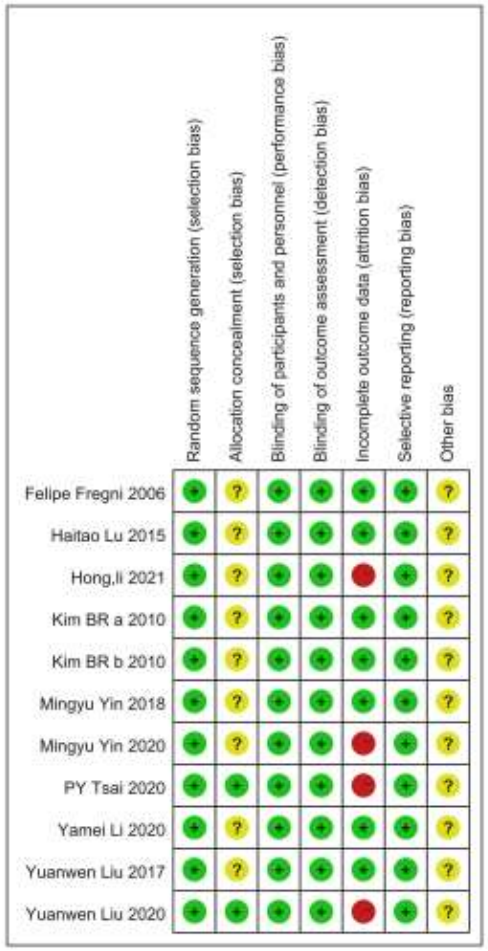


Fig. 8. The risks of bias of included studies based on the Cochrane's handbook. The bias risk of each item was further evaluated as "low risk (+)", "unclear risk (?)", and "high risk (-)".

2.3. Methodological quality assessment

Two researchers independently evaluated the quality of included literature in accordance with Cochrane Systematic Review Manual, including the generation of randomized sequence, concealment assignment, blindness, integrity of data, and selective reporting of results. The bias risk of each item was further evaluated as "low risk (+)", "unclear risk (?)", and "high risk (-)".

評讀的面向	
✓	使用GRADE評讀systematic reviews
	當2位獨立評讀人員文獻出現分歧，會再由第3人評估

是	
不明確	V
否	

(A)研究結果可信嗎?

5.如果作者將研究結果進行合併，這樣的合併是否合理?

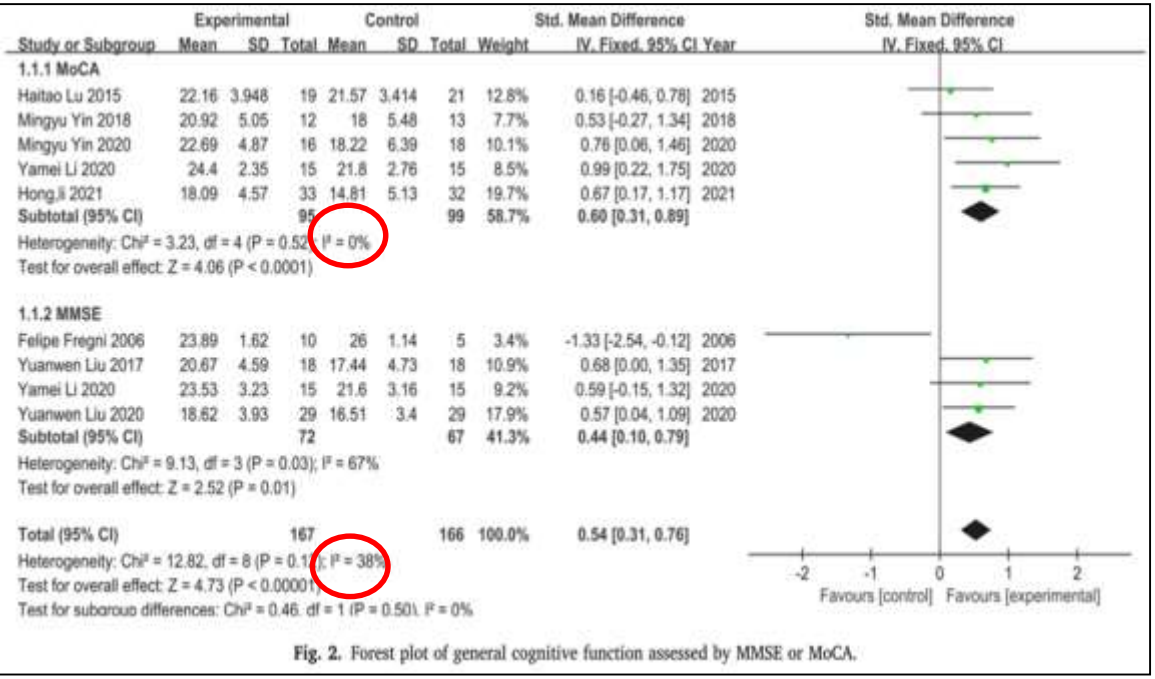
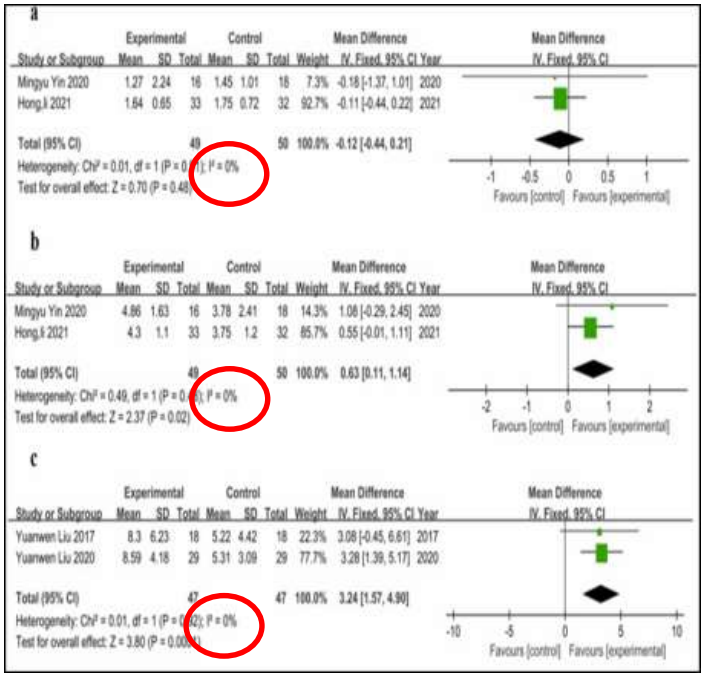


Fig. 2. Forest plot of general cognitive function assessed by MMSE or MoCA.

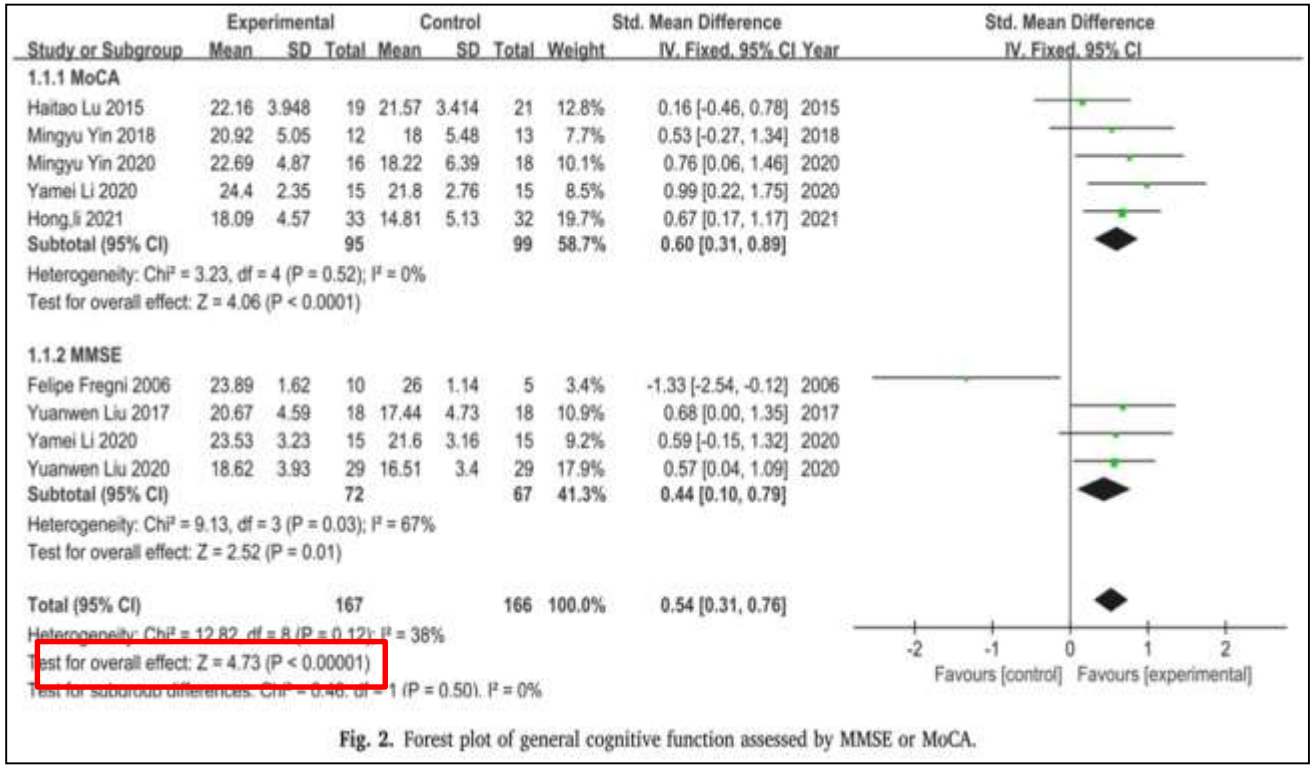


是	V
不明確	
否	

(B)研究結果為何?

6. 這篇系統性文獻回顧的整體結果為何？

(1) global cognition



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
1.1.1 MoCA									
Haitao Lu 2015	22.16	3.948	19	21.57	3.414	21	12.8%	0.16 [-0.46, 0.78]	2015
Mingyu Yin 2018	20.92	5.05	12	18	5.48	13	7.7%	0.53 [-0.27, 1.34]	2018
Mingyu Yin 2020	22.69	4.87	16	18.22	6.39	18	10.1%	0.76 [0.06, 1.46]	2020
Yamei Li 2020	24.4	2.35	15	21.8	2.76	15	8.5%	0.99 [0.22, 1.75]	2020
Hong,li 2021	18.09	4.57	33	14.81	5.13	32	19.7%	0.67 [0.17, 1.17]	2021
Subtotal (95% CI)			**95**			**99**	**58.7%**	**0.60 [0.31, 0.89]**	
Heterogeneity: Chi² = 3.23, df = 4 (P = 0.52); I² = 0%									
Test for overall effect: Z = 4.06 (P < 0.0001)									
1.1.2 MMSE									
Felipe Fregni 2006	23.89	1.62	10	26	1.14	5	3.4%	-1.33 [-2.54, -0.12]	2006
Yuanwen Liu 2017	20.67	4.59	18	17.44	4.73	18	10.9%	0.68 [0.00, 1.35]	2017
Yamei Li 2020	23.53	3.23	15	21.6	3.16	15	9.2%	0.59 [-0.15, 1.32]	2020
Yuanwen Liu 2020	18.62	3.93	29	16.51	3.4	29	17.9%	0.57 [0.04, 1.09]	2020
Subtotal (95% CI)			**72**			**67**	**41.3%**	**0.44 [0.10, 0.79]**	
Heterogeneity: Chi² = 9.13, df = 3 (P = 0.03); I² = 67%									
Test for overall effect: Z = 2.52 (P = 0.01)									
Total (95% CI)			**167**			**166**	**100.0%**	**0.54 [0.31, 0.76]**	
Heterogeneity: Chi² = 12.82, df = 8 (P = 0.12); I² = 38%									
Test for overall effect: Z = 4.73 (P < 0.00001)									
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.50), I² = 0%									

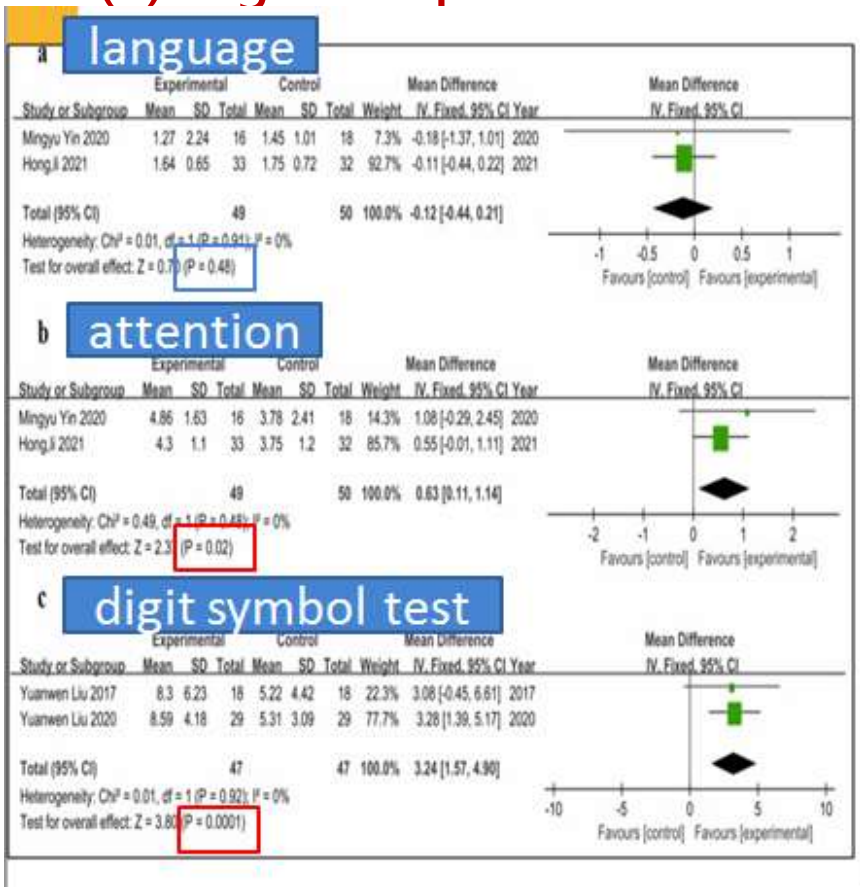
Fig. 2. Forest plot of general cognitive function assessed by MMSE or MoCA.

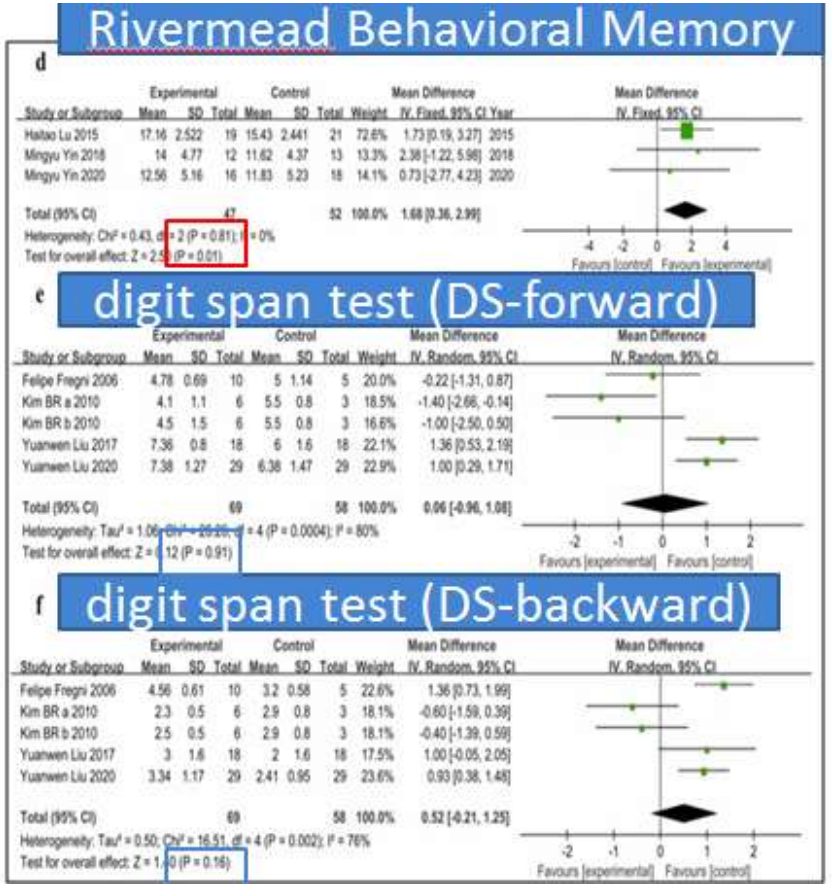
其結果顯示: 對於腦中風病人rTMS介入組相較於控制組的認知有顯著提升

(B)研究結果為何?

6. 這篇系統性文獻回顧的整體結果為何？

(2)Cognition performance





其結果顯示:對於腦中風病人rTMS介入組相較於控制組的認知表現(注意力、數字符號、行為記憶)有顯著提升

(B)研究結果為何?

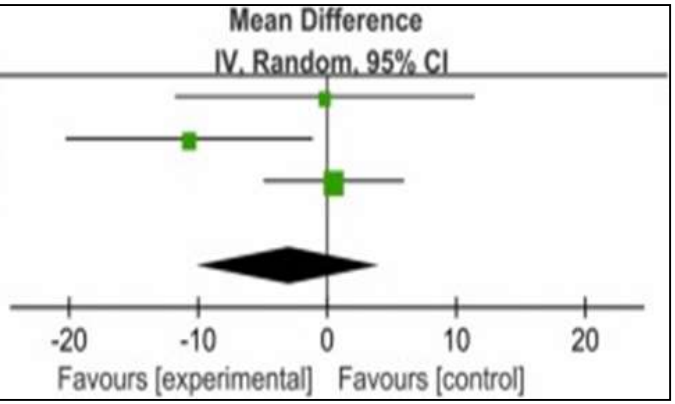
6. 這篇系統性文獻回顧的整體結果為何？

(3) depression

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Kim BR a 2010	13.8	8.5	6	14	8.3	3	23.6%	-0.20 [-11.80, 11.40]	2010
Kim BR b 2010	3.3	2.3	6	14	8.3	3	29.6%	-10.70 [-20.27, -1.13]	2010
PY Tsai 2020	8.3	6.5	11	7.8	7.6	15	46.8%	0.50 [-4.94, 5.94]	2020
Total (95% CI)			23			21	100.0%	-2.98 [-10.05, 4.09]	

Heterogeneity: Tau² = 20.11; Chi² = 4.08, df = 2 (P = 0.13); I² = 51%

Test for overall effect: Z = 0.83 (P = 0.41)



其結果顯示: 對於腦中風病人rTMS介入組相較於控制組的憂鬱無顯著改善

(B)研究結果為何?

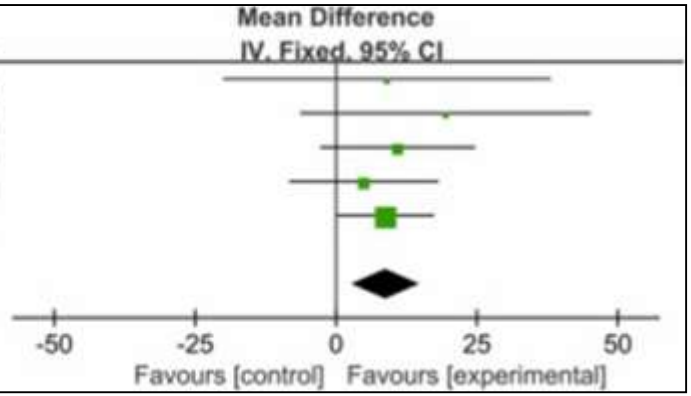
6. 這篇系統性文獻回顧的整體結果為何？

(4) the ability of daily living

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Kim BR a 2010	69.8	24.3	6	60.8	19.1	3	4.4%	9.00 [-20.07, 38.07]	2010
Kim BR b 2010	80.2	17.5	6	60.8	19.1	3	5.6%	19.40 [-6.35, 45.15]	2010
Mingyu Yin 2018	61.92	18.46	12	51	16.52	13	19.4%	10.92 [-2.85, 24.69]	2018
Mingyu Yin 2020	61.81	17.67	16	56.89	21.73	18	21.0%	4.92 [-8.34, 18.18]	2020
Hong,li 2021	62.21	16.58	33	53.41	18.71	32	49.7%	8.80 [0.20, 17.40]	2021
Total (95% CI)			73			69	100.0%	9.00 [2.93, 15.06]	

Heterogeneity: Chi² = 1.07, df = 4 (P = 0.90); I² = 0%

Test for overall effect: Z = 2.91 (P = 0.004)

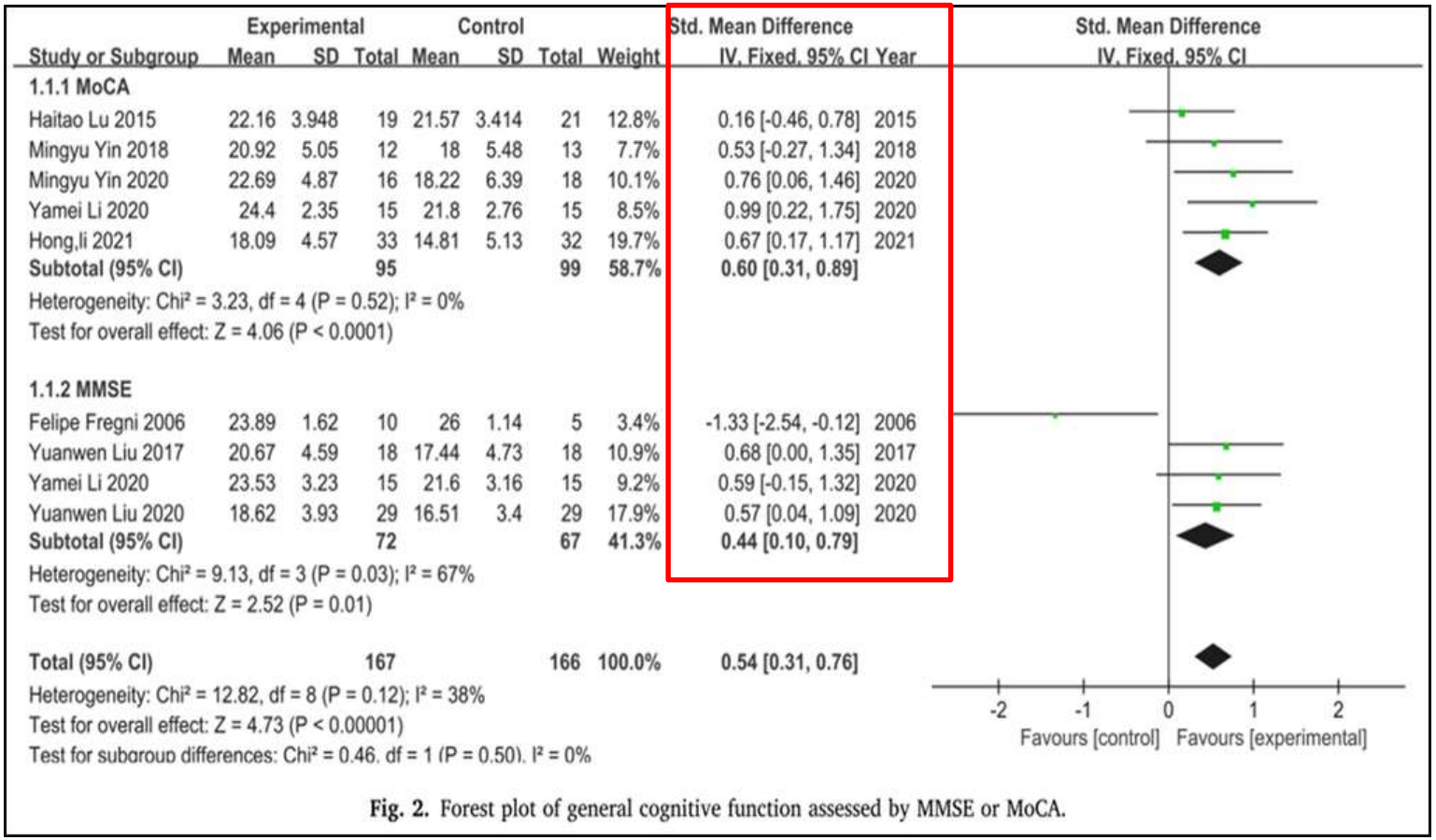


其結果顯示:對於腦中風病人rTMS介入組相較於控制組的日常生活能力有顯著提升

(B)研究結果為何?

7. 結果精準嗎？

(1) global cognition



Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Year
1.1.1 MoCA									
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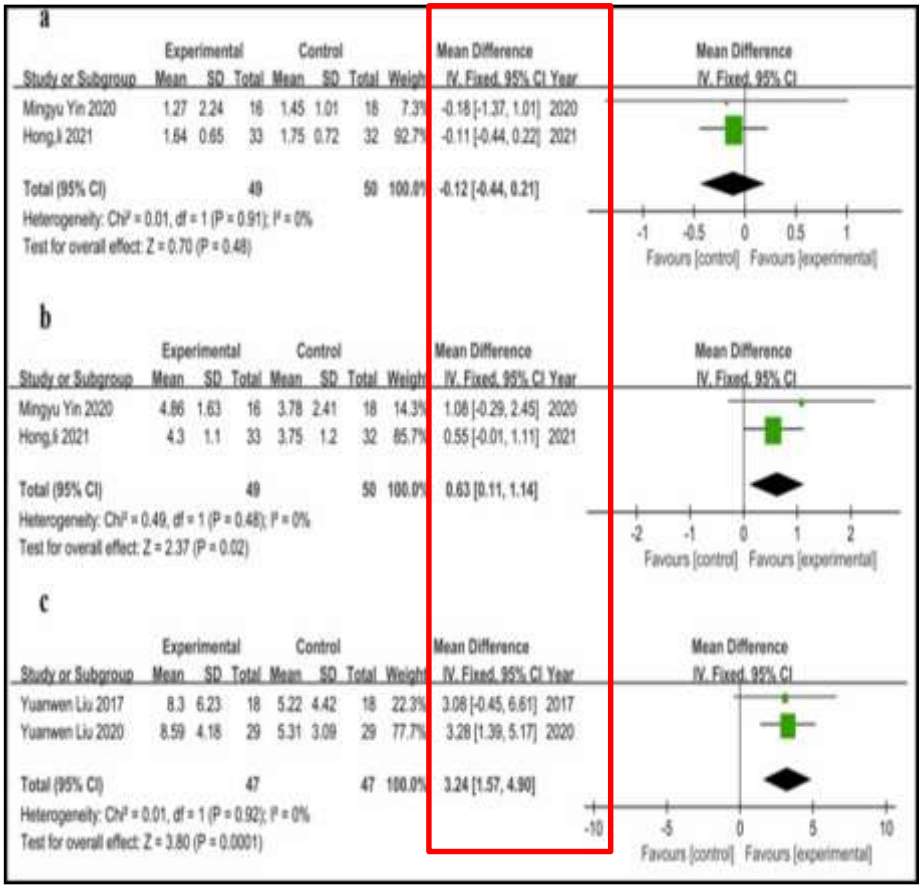
Mingyu Yin 2020	22.69	4.87	16	18.22	6.39	18	10.1%	0.76 [0.06, 1.46]	2020
Yamei Li 2020	24.4	2.35	15	21.8	2.76	15	8.5%	0.99 [0.22, 1.75]	2020
Hong,li 2021	18.09	4.57	33	14.81	5.13	32	19.7%	0.67 [0.17, 1.17]	2021
Subtotal (95% CI)			**95**			**99**	**58.7%**	**0.60 [0.31, 0.89]**	
Heterogeneity: Chi² = 3.23, df = 4 (P = 0.52); I² = 0%									
Test for overall effect: Z = 4.06 (P < 0.0001)									
1.1.2 MMSE									
Felipe Fregni 2006	23.89	1.62	10	26	1.14	5	3.4%	-1.33 [-2.54, -0.12]	2006
Yuanwen Liu 2017	20.67	4.59	18	17.44	4.73	18	10.9%	0.68 [0.00, 1.35]	2017
Yamei Li 2020	23.53	3.23	15	21.6	3.16	15	9.2%	0.59 [-0.15, 1.32]	2020
Yuanwen Liu 2020	18.62	3.93	29	16.51	3.4	29	17.9%	0.57 [0.04, 1.09]	2020
Subtotal (95% CI)			**72**			**67**	**41.3%**	**0.44 [0.10, 0.79]**	
Heterogeneity: Chi² = 9.13, df = 3 (P = 0.03); I² = 67%									
Test for overall effect: Z = 2.52 (P = 0.01)									
Total (95% CI)			**167**			**166**	**100.0%**	**0.54 [0.31, 0.76]**	
Heterogeneity: Chi² = 12.82, df = 8 (P = 0.12); I² = 38%									
Test for overall effect: Z = 4.73 (P < 0.00001)									
Test for subgroup differences: Chi² = 0.46, df = 1 (P = 0.50), I² = 0%									

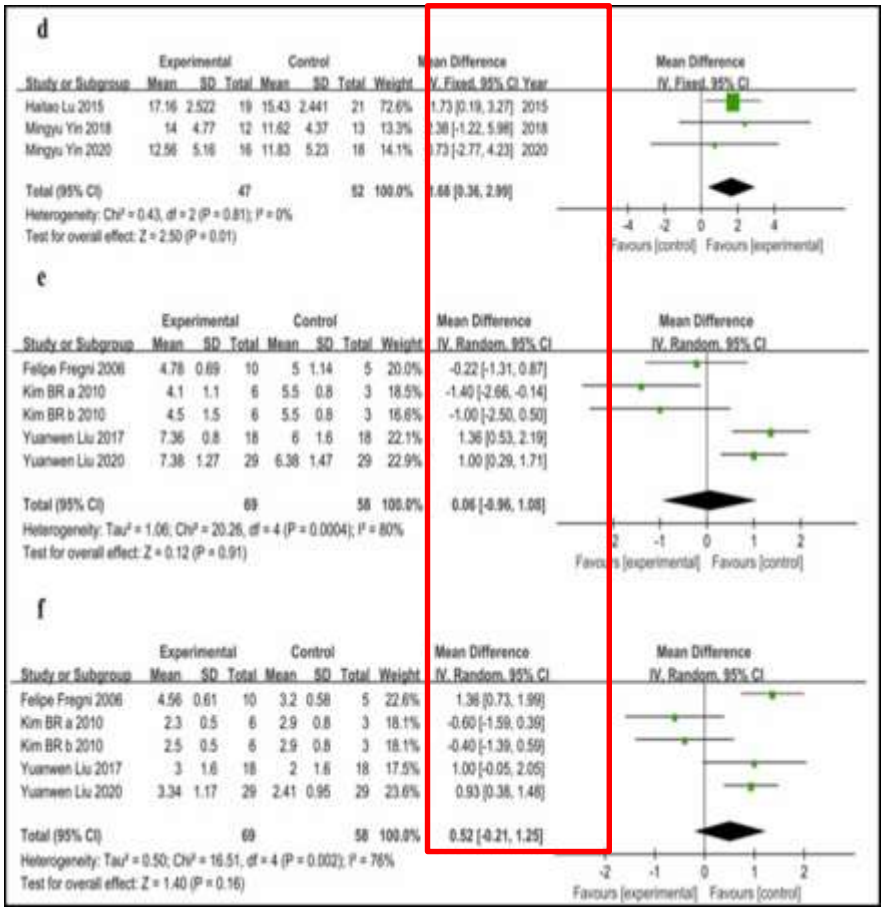
Fig. 2. Forest plot of general cognitive function assessed by MMSE or MoCA.

(B)研究結果為何?

7. 結果精準嗎？

(2)Cognition performance





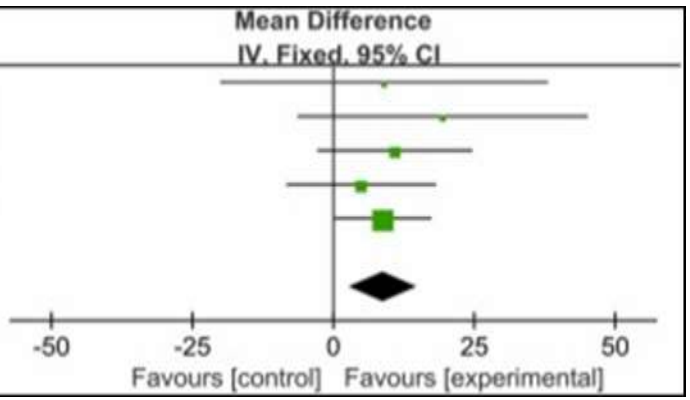
(B)研究結果為何?

7. 結果精準嗎？

(3) the ability of daily living

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Kim BR a 2010	69.8	24.3	6	60.8	19.1	3	4.4%	9.00 [-20.07, 38.07]	2010
Kim BR b 2010	80.2	17.5	6	60.8	19.1	3	5.6%	19.40 [-6.35, 45.15]	2010
Mingyu Yin 2018	61.92	18.46	12	51	16.52	13	19.4%	10.92 [-2.85, 24.69]	2018
Mingyu Yin 2020	61.81	17.67	16	56.89	21.73	18	21.0%	4.92 [-8.34, 18.18]	2020
Hong,li 2021	62.21	16.58	33	53.41	18.71	32	49.7%	8.80 [0.20, 17.40]	2021
Total (95% CI)			**73**			**69**	**100.0%**	**9.00 [2.93, 15.06]**	

Heterogeneity: Chi² = 1.07, df = 4 (P = 0.90); I² = 0%
Test for overall effect: Z = 2.91 (P = 0.004)



(C)研究結果對於當地病人有幫助嗎?

8. 此研究結果是否可應用到當地的族群？

大部分是中國,少部分是南美及韓國

Table 1
The basic characteristics of the included research.

rTMS studies	Age (yrs)	Male/ Female	Education (yrs)	Disease course (days)	Ischemic/ Hemorrhage
	Active				
Po-Yi Tsai (2020) [25]	57.45 ± 12.3	9/2	14 ± 2.8	33.27 ± 26.4	3/8
Felipe Fregni (2006) [26]	57.70 ± 11.27	8/2	–	105.6 ± 87.9	–
Kim BR (2010) [27]	53.5 ± 16.9	4/2	–	241.2 ± 42.5	4/2
	68.3 ± 7.4	2/4	–	404.4 ± 71.7	5/1
Haitao Lu (2015) [31]	42.5 ± 12.3	12/7	12.8 ± 3.8	67 (30 , 365)	8/11
Yuanwen Liu (2017) [32]	65.33 ± 7.05	11/7	7.56 ± 3.81	253.2 ± 53.7	13/5
Mingyu Yin (2018) [33]	58.58 ± 11.98	11/1	9.54 ± 3.24	59.83 ± 30.59	10/2
Yamei Li (2020) [34]	65.47 ± 3.68	7/8	19.13 ± 7.95	22.73 ± 8.05	–
Yuanwen Liu (2020) [35]	58.55 ± 6.24	10/19	9.76 ± 2.80	263.7 ± 55.2	20/9
Mingyu Yin (2020) [36]	56.69 ± 12.92	14/2	10.03 ± 4.15	52 (38.25 , 98.75)	11/5
Hong , Li (2021) [37]	61.79 ± 5.51	21/12	10.21 ± 1.60	28.64 ± 12.60	22/11

Table 2
rTMS parameters of included records.

Study	Stimulation Position	Intensity	Total pulse	Duration
Hong , Li (2021)	the contralateral DLPFC	1hz	1000 pulse	5 days per week for 4 weeks (total 20 times)
Po-Yi Tsai (2020)	the left DLPFC	5hz	600 pulse	5 days per week for 2 weeks (total 10 times)
Mingyu Yin (2020)	the left DLPFC	10hz	2000 pulse	5 days per week for 4 weeks (total 20 times)
Yuanwen Liu (2020)	the left DLPFC	10hz	700 pulse	5 days per week for 4 weeks (total 20 times)
Yamei Li (2020)	the left DLPFC	5hz	2000 pulse	5 days per week for 3weeks (total 15 times)
Mingyu Yin (2018)	the left DLPFC	10hz	2000 pulse	5 days per week for 4 weeks (total 20 times)
Yuanwen Liu (2017)	the left DLPFC	10hz	700 pulse	5 days per week for 4 weeks (total 20 times)
Haitao Lu (2015)	the right DLPFC	1hz	600 pulse	5 days per week for 4 weeks (total 20 times)
Kim BR (2010)	the left DLPFC	10hz	450 pulse	5 days per week for 2 weeks (total 10 times)
	the left DLPFC	1hz	900 pulse	5 days per week for 2 weeks (total 10 times)
Felipe Fregni (2006)	the FDI cortical area	5hz	1200 pulse	5 days per week for 1 weeks (total 5 times)

評讀的面向	
✓	病人與本地族群亞洲與非亞洲文獻與人次無統計學上差異
✓	使用器材部分是相同
	訓練模式, 時間, 頻率不一定

是	
不明確	V
否	

(C)研究結果對於當地病人有幫助嗎?

9. 是否所有重要的臨床結果都有被考量到？

評讀的面向	
✓	Global cognition
✓	Cognition performance
	Depression
✓	Ability of daily living

是	
不明確	V
否	

(C)研究結果對於當地病人有幫助嗎?

10.付出的傷害和花費換得介入措施所產生的益處是否值得？

評讀的面向	
✓	高費用
	傷害
✓	時間成本、便利性

是	
不明確	V
否	

重複經顱磁刺激是否可改善中風病人的認知能力?

同意 : 14位

不同意 : 0 位

需要更多文獻支持 : 12位

感謝聆聽，請多指教!