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Memory Impairment Following Electroconvulsive Therapy in Chinese Patients with Schizophrenia: Meta-Analysis of Randomized Controlled Trials

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Memory impairment following electroconvulsive therapy in Chinese patients with schizophrenia: meta-analysis of randomized controlled trials

Running title: ECT and memory impairment

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ABSTRACT

PURPOSE: To evaluate memory impairment associated with electroconvulsive therapy (ECT)-antipsychotic (AP) combination in comparison to AP monotherapy in schizophrenia.

DESIGN AND METHODS: A systematic literature search of RCTs was performed.

FINDINGS: Eleven RCTs that compared ECT-AP combination (n=508) with AP monotherapy (n=510) were analyzed. ECT-AP combination was associated with greater impairment than AP monotherapy in (1) endpoint memory quotient (MQ) of the Wechsler Memory Scale-Revised at the end of the ECT course; (2) picture recall, counting, recognition, associative learning of the WMS. However, no group difference was found in MQ at 1 and 2 weeks post-ECT.

PRACTICE IMPLICATIONS: The ECT-AP combination was associated with greater transient memory impairment compared to AP monotherapy.

Trial registration: CRD42014006689 (PROSPERO)

Key words: ECT-antipsychotic combination; memory impairment, meta-analysis

INTRODUCTION

Electroconvulsive therapy (ECT) has been used to treat schizophrenia since its introduction (Chanpattana et al., 1999). Around 2.9% to 36% of schizophrenia patients received ECT in the Western world (Chanpattana, Chakrabhand, Buppanharun, & Sackeim, 2000; Wang et al., 2015). In China ECT is commonly used; in recent years up to 55.2% of inpatients with schizophrenia received ECT (Wang et al., 2015).

ECT increases the risk for cognitive impairment, particularly for memory memory disturbances. Most case reports and series (Bertagnoli & Borchardt, 1990; Consoli et al., 2009; Gambill & McLean, 1983; Keller, Drexler, & Lichtenberg, 2009) have found that memory impairment caused by ECT is relatively mild and transient. In contrast, randomized controlled trials (RCTs) (Jiang et al., 2009; Kou et al., 2013; Y. D. Li, Tang, Song, & Huang, 2012; Z. X. Li, 2015; Yang, Jiang, Zhu, & Lv, 2013; Ye, Wu, & Yang, 2009; F. Yu et al., 2012; Q. Yu, Wang, Chen, & Zhuo, 2015; Zhang, Liu, Hu, & Zhou, 2010; C. X. Zhou, Xiong, & Fu, 2015; H. J. Zhou, Mao, Chen, Song, & Shi, 2009) comparing ECT-antipsychotic (AP) combinations with AP

monotherapy in schizophrenia reported conflicting findings in terms of memory impairment.

Recognition of memory impairment early in the course of ECT is important because modifying the course – for instance giving ECT only twice a week or reducing the stimulus charge - could prevent sustained memory impairment. Nurses, who spend more time with patients than any other health professionals, are best placed to identify early signs of cognitive impairment.

A thorough search of the literature could not locate any systematic review or meta-analysis specifically examining memory impairment-caused by ECT in schizophrenia. Further, China has one of the largest population on ECT use worldwide (Wang et al., 2015), therefore this study systematically searched English- and Chinese-language databases to conduct a comprehensive meta-analysis of RCTs with a focus on memory impairment caused by ECT in schizophrenia patients.

METHODS

ECT in China

In China ECT is mainly recommended for the treatment of bipolar disorder, major depressive disorder and schizophrenia, particularly for patients with severe suicidal or aggressive behavior and catatonia (Chinese Medical Association, 2003; Shen, 2009). Treatment guidelines recommend 6-12 sessions in a course under general anesthesia for patients (Shen, 2009). Propofol is the most frequently used anaesthetic in most hospitals together with succinylcholine and oxygenation. A brief pulse wave device with bitemporal electrode placement is most commonly used.

Search Strategy and Selection Criteria

Two independent authors (ZW and TG) searched PubMed, PsycINFO, Embase, Cochrane Library databases, the Cochrane Controlled Trials Register, CJN, WanFang and CBM for RCTs concerning ECT-AP combination compared with AP for memory impairment in Chinese patients with schizophrenia from inception of the database until October 2015 using the following search terms: (Schizophrenic Disorder OR Disorder, Schizophrenic OR Schizophrenic Disorders OR Schizophrenia OR Dementia Praecox) AND

(ECT OR Electric Convulsive Therap* OR Therap*, Electric Convulsive OR Electroshock Therap* OR Convulsive Therap*, Electric OR Electroconvulsive Therapy OR Electroconvulsive Therapies OR Therap*, Electroconvulsive OR Electric Shock Therap* OR Shock Therap*, Electric OR Therap*, Electric Shock OR Therap*, Electroshock) AND (China OR Chinese). The keywords were used in combination with the Bolean operators of AND, OR and NOT. The electronic search was supplemented by a manual review of reference list from eligible publications and relevant reviews. Whenever data were missing for the meta-analysis or available data were significantly skewed, authors were contacted for additional information.

According to *PICOS* acronym, we identified following selection criteria: Participants (*P*): adult patients (≥18 years) with schizophrenia with any diagnose criteria. Intervention (*I*): ECT plus AP. Comparison (*C*): AP monotherapy. Outcomes (*O*): memory impairment and executive function assessed using the Wechsler Memory Scale-Revised, Chinese version (WMS-RC) (Gong, Jiang, Deng, Dai, & Zhou, 1989) and Wisconsin Card Sorting Test (WCST) (Heaton, Chelune, Talley, Kay, & Curtiss, 1981) with meta-analyzable data. Study design (*S*): RCT. Case series, non-randomized

studies, and non-original research (reviews and meta-analyses) were excluded.

Data extraction and Outcome Measures

Data extraction based on intent to treat (ITT) analysis if provided; data synthesis, and assessment of bias were conducted independently by two authors. Inconsistencies were resolved by consensus or involvement of a third reviewer.

The primary outcome measure was memory quotient (MQ) assessed by the WMS-RC at the end of the ECT course. The key secondary outcomes were picture recall, counting, recognition, associative learning of WMS-RC, executive function, all-caused discontinuation, and adverse drug reactions (ADRs).

Assessment of study quality

The quality of each study was also assessed with the Jadad scale that assesses study quality on a 5-point scale along the following five domains:

"randomization," "double blinding," "description withdrawals and dropouts," dropouts," "generation of random numbers," and "allocation concealment" (Jadad et al., 1996). The criteria of high and low quality were defined as Jadad score ≥3 and <3, respectively.

Data synthesis and statistical analyses

The meta-analysis was performed using the Review Manager Version 5.3 software (http://www.cochrane.org), STATA version 12.0 software (http://www.stata.com) and Comprehensive Meta-Analysis version 2 software (http://www.meta-analysis.com). To combine studies, the random effects model (DerSimonian & Laird, 1986) was used in all cases. For continuous data and dichotomous data, standard mean difference (SMD) and risk ratio (RR) ±95% CIs was calculated, respectively. Furthermore, the number-needed-to-harm (NNH) by dividing 1 by the risk difference was calculated when RR was significant. In case of $I^2 \geq 50\%$ (Higgins & Thompson, 2002) for primary outcome, a sensitive analysis was conducted by excluding one outlying study (Kou et al., 2013) (SMD=-4.21).

For primary outcome, publication bias was assessed using funnel plots, Egger's intercept (Egger, Davey Smith, Schneider, & Minder, 1997), Duval and Tweedie's trim-and-fill procedure (Duval & Tweedie, 2000) and fail-safe method (Rosenthal, 1979) that estimates the number of studies needed to change the findings. All statistical differences were considered significant at the level of $p<0.05$.

RESULTS

Literature search

By the initial database searches and other sources, a total of 408 potentially relevant articles were ascertained. The EndNote software (version 7.1) identified 87 studies as duplicates. Finally, 11 RCTs (Table 1) met the selection criteria for meta-analysis after screening their titles and abstracts and a full text review. (Figure 1).

RCTs and patient characteristics

A total of 11 RCTs (Table 1) comprising 1,018 patients (sample size range=40-246, median=63) compared ECT-AP combination (n=508) with AP monotherapy (n=510). Patients with available data were aged 38.1±7.7 years (range=25.6-49.2 years, median=38.3 years). The ECT course lasted 6.1±3.4 weeks (range=2 to 12 weeks, median=6.0 weeks); 43.2±15.8% was male (range=0%-55.2%, median=47.0) and the mean illness duration (9 RCTs) was 7.8±6.1 years (range=0.5-20.2 years, median=7.8 years). ECT courses had 11.3±3.8 treatments (range=6.0-18.0 treatments, median=10.0 treatments).

Quality assessment

The Jadad score was 2.0±0.6 (range=1-3, median=2). Two RCTs were classified as high quality and the remaining 9 RCTs were low quality.

Neurocognitive functioning

Primary Outcomes: ECT-AP combination (n=110) was associated with greater impairment compared to AP monotherapy (n=110) regarding the

MQ of WMS-RC at the end of the ECT course [SMD:-1.43 (95%CI:-2.80, -0.05), P=0.04; I^2=95%, Figure 2]. Results remained significant after removed an outlier study [SMD:-0.53 (95%CI:-0.97, -0.08), P=0.02; I^2=48%]. However, there are no significant group differences in the MQ total score at 1 and 2 weeks post-ECT [SMD:-0.21 to -0.12 (95%CI:-0.66, 0.39), P=0.37 to 0.65; I^2=77%, Figure 2]. Only 4 RCTs were meta analyzed, thus funnel plot analysis to show publication bias could not be conducted.

Secondary Outcomes: ECT-AP combination was associated with more impairment compared to AP monotherapy in the WMS-RC picture recall, counting, recognition and associative learning [SMD:-1.60 to -0.95 (95%CI:-2.54, -0.50), P=0.0001 to 0.001; I^2=46% to 85%, Figure 3] at the end of the ECT course. In contrast, ECT-AP combination was significantly superior to AP monotherapy regarding WCST response administered [SMD:-0.46 (95%CI:-0.75, -0.16), P=0.002; I^2=38%, Figure 4] and response errors [SMD:-0.35 (95%CI:-0.67, -0.04), P=0.03; I^2=0%, Figure 4], but not for response corrects, perseverative errors, non-perseverative errors and categories complete [SMD:-0.23 to 0.21

(95%CI:-1.25, 0.89), P=0.19 to 0.74; I^2=0% to 95%, Figure 4] between the two groups.

Treatment Discontinuation and ADRs

All-cause discontinuation was similar between ECT-AP combination (n=157) vs. AP monotherapy (n=158) (RR=1.38, (95%CI: 0.09, 20.24), P=0.81, I^2=33%; Supplemental Figure 1). Headache (15.1% vs 0%; RR=17.27, P=0.0006, NNH=7, 95%CI=5-11) and electroencephalogram abnormalities (36.1% vs 8.1%; RR=4.45, P=0.001, NNH=4, 95%CI=2-7) were more prevalent in the ECT-AP group compared to the AP monotherapy. Meta-analysis of akathisia, blurred vision, dry mouth, drowsiness, dizziness, dizziness, weight gain, electrocardiographic abnormalities, hypersalivation, rigidity, tremor, insomnia, tachycardia, constipation, elevated liver enzymes and nausea/vomiting did not significantly differ between the two groups (Supplemental Figure 2).

DISCUSSION

In this first meta-analysis of 11 RCTs with a total of 1,018 patients suffering from schizophrenia, we found that adjunctive ECT with APs was associated with worse MQ than the control group at the end of the ECT course. However, there was no significant difference between groups regarding MQ at 1 and 2 weeks post-ECT. Furthermore, meta-analysis of WMS-RC picture recall, counting, recognition and associative learning showed that the ECT-AP combination were associated with worse outcomes compared to AP monotherapy at the end of the ECT course.

The mechanism of ECT for memory impairment is still unclear (Rami et al., 2008). Possible mechanisms of memory impairment associated with ECT may result from: (1) an excessive release of excitatory amino acids and the activation of their receptors, such as N-methyl-D-aspartic acid (NMDA); (2) increasing cerebral blood pressure and reductions in regional cerebral blood (Rami et al., 2008).

Several limitations of this study need to be considered. First, the mean Jadad score of meta-analyzed studies ranged between 1 and 3, which may potentially influence the conclusions of this study. Second, although the total sample size of 11 RCTs was moderate at 1,018 since more than 1,000

patients are considered necessary for robust results in a meta-analysis (Trikalinos et al., 2004), the information in most trials was limited or incomplete, such as electrode placement and stimulation dosing methods. In addition, 4 RCTs (n=220) used WMS to assess memory impairment resulting in a lack of meaningful subgroup and meta-regression analyses for effect size moderators. Third, the significant heterogeneity (I^2>50%) of meta-analytic results of the endpoint MQ revealed the effect of relevant moderator and mediator variables. Fourth, information related to neurocognition, such as education level and learning effect of cognitive assessment, were incomplete in the studies, therefore their impact on the results could not be explored. Finally, Rami et al (Rami et al., 2004) reported that maintenance ECT (session numbers=27.2) patients did not show more severe memory impairment than AP monotherapy. The mean session number was 11.3 in our study, thus, our findings could not be generalized to maintenance ECT.

CONCLUSIONS

The evidence from this meta-analysis of 11 RCTs (n=1,018) shows that a subset of patients with schizophrenia could have significant memory impairment caused by adjunctive ECT in combination with APs. When prescribing ECT, the possibility of memory disturbance should be considered against the expected therapeutic effects of the treatment. However, the adverse cognitive effects appear to resolve at 1-2 weeks post-ECT.

Results of this study have implications for the care of patients treated with ECT. Early recognition of memory disturbances is critical in preventing long-term cognitive impairment. Frontline staff particularly nurses who spend the most time observing and communicating with patients have a crucial role in detecting early signs of memory impairment. Recognition of ECT-related memory impairment could be enhanced if psychiatric nurses would pay particular attention to memory disturbances and would conduct brief bedside cognitive assessment in case impending cognitive impairment is suspected.

DISCLOSURE OF INTEREST

The authors declare that they have no conflicts of interest concerning this article.

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Table 1. Characteristics of the RCTs and study samples

	Country	N[a]	Design			Schizophrenia patients					ECT			Co
			Duration (weeks)[b]	Blinding	APs	Age (yrs)	Education (yrs)	Male (%)	Criteria	Illness duration (yrs)	Bilateral/ unilateral	Electricity dose	Section (times)	
	China	69	12	Open-label	RIS	39.0	6.9	55.2	CCMD-3	12.5	NR	NR	8-12	W
	China	40	3	Open-label	APs[c]	18-39	NR	38	CCMD-3	0.5-15	Unilateral	100 mA	6-9	W
	China	63	4	Open-label	OLA	42.6	NR	37	CCMD-3	20.2	Bilateral	Age*80%	9	WM
0	China	246	7	Rater-masked	CLO	41.3	12.2	42	CCMD-3	8.2	Bilateral	NR	15	W
	China	60	12	Rater-masked	APs[d]	33.1	NR	55	CCMD-3	10.7	Bilateral	Age*80%	18	W
	China	60	2	Open-label	RIS	30.3	NR	43	DSM-IV	2.5	NR	NR	6	WM
	China	60	3-4	Open-label	RIS/OLA	33.8	NR	0	ICD-10	5.2	Bilateral	Age*5c	10	W
	China	72	6	Open-label	APs[c]	48.8	NR	54	CCMD-3	5-13	NR	NR	≤12	W
	China	60	8	Rater masked	PAL	37.5	NR	47	CCMD-3	NR	NR	NR	16	W
	China	188	6	Open-label	OLA	49.2	NR	53	CCMD-3	0.7	Unilateral	NR	13	W
	China	100	4	Open-label	APs[c]	25.6	NR	51	NR	2.4	Bilateral	NR	8	W

ects the total sample size recruited patients in RCTs.

on at the end of the ECT course.

he detail use of antipsychotic.

ne, chlorpromazine, perphenazine, risperidone, sulpiride, and paliperidone.

otics; CLO=clozapine; CCMD-3 = China's mental disorder classification and diagnosis standard 3th edition; DSM-IV = Diagnostic and Statistical Manual of Mental Disorder
Test; ECT = electroconvulsive therapy; NR = not report; OLZ = olanzapine; PAL= paliperidone; RCT = randomized controlled trial; RIS = risperidone; ICD-10 = the 10th R
istical Classification of Diseases and Related Health Problems; WCST = Wisconsin Card Sorting Test; WMS-RC = Wechsler Memory Scale-Revised, Chinese version; yr

Figure 1. PRISMA flow diagram

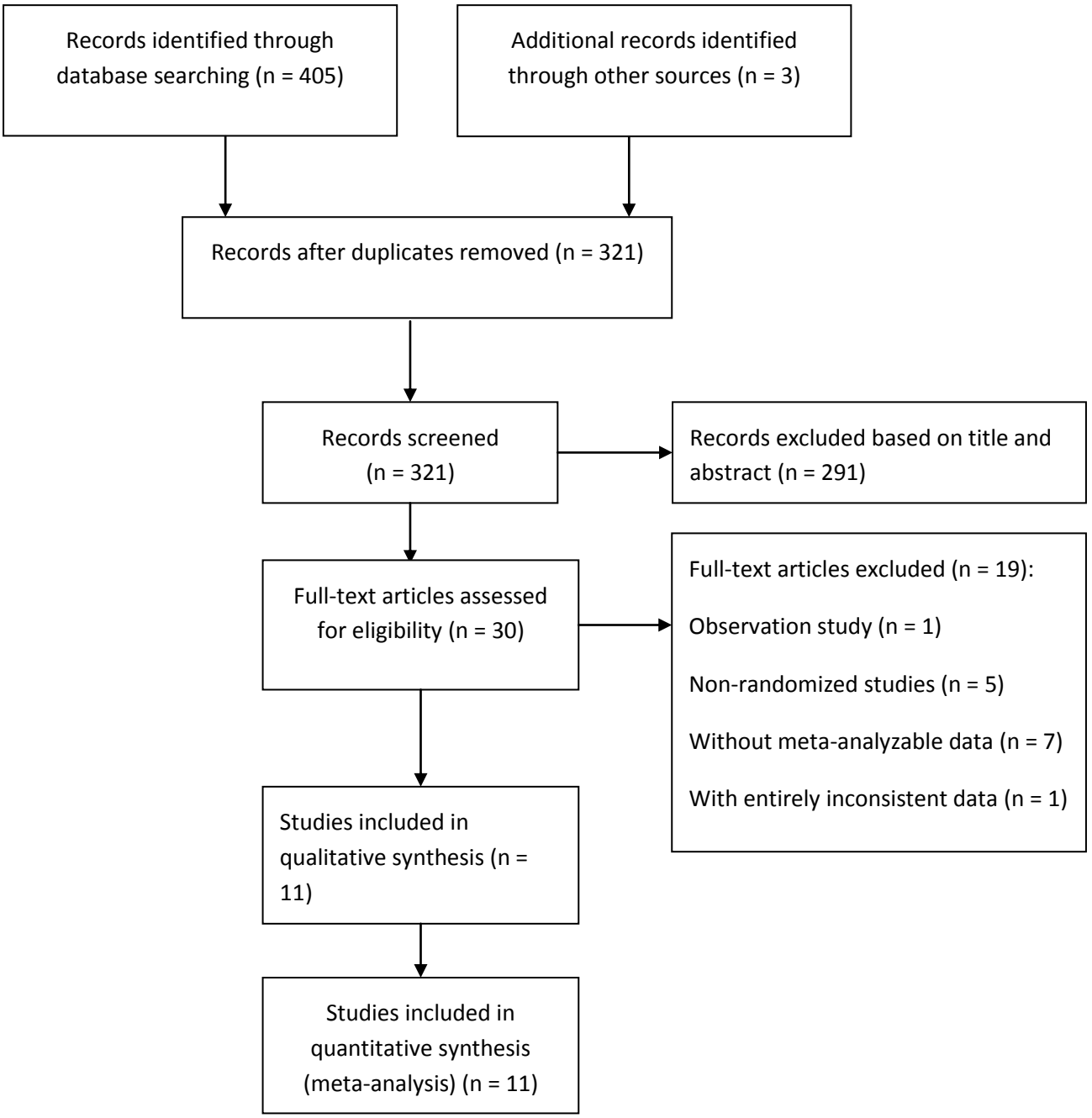


Figure 2. Electroconvulsive therapy (ECT)-related memory impairment in schizophrenia: forest plot for memory quotient assessed by Wechsler Memory Scale-Revised, Chinese version

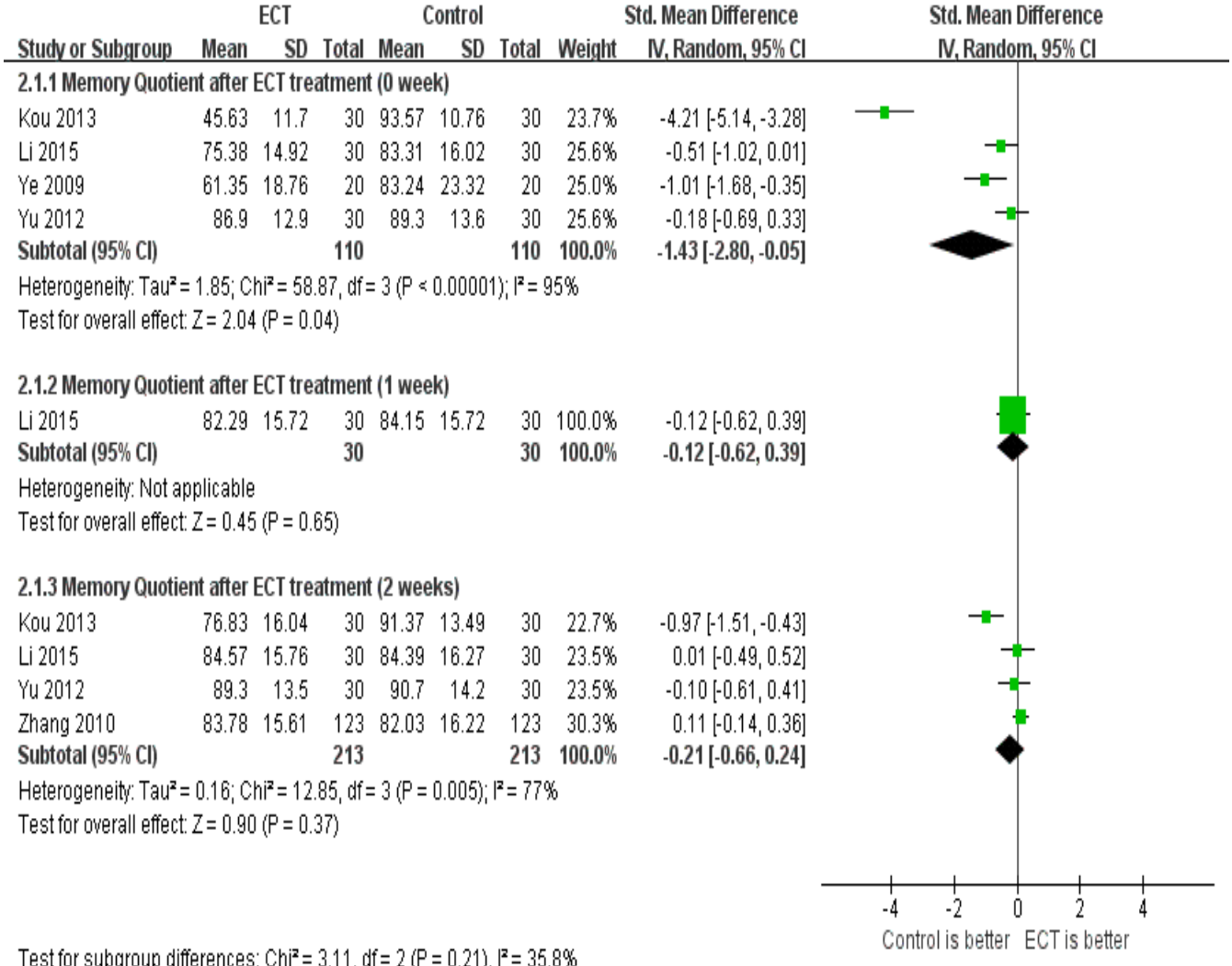


Figure 3. Electroconvulsive therapy (ECT)-related memory impairment in schizophrenia: forest plot for picture recall, counting, recognition, associative learning assessed by Wechsler Memory Scale-Revised, Chinese version at the end of ECT course

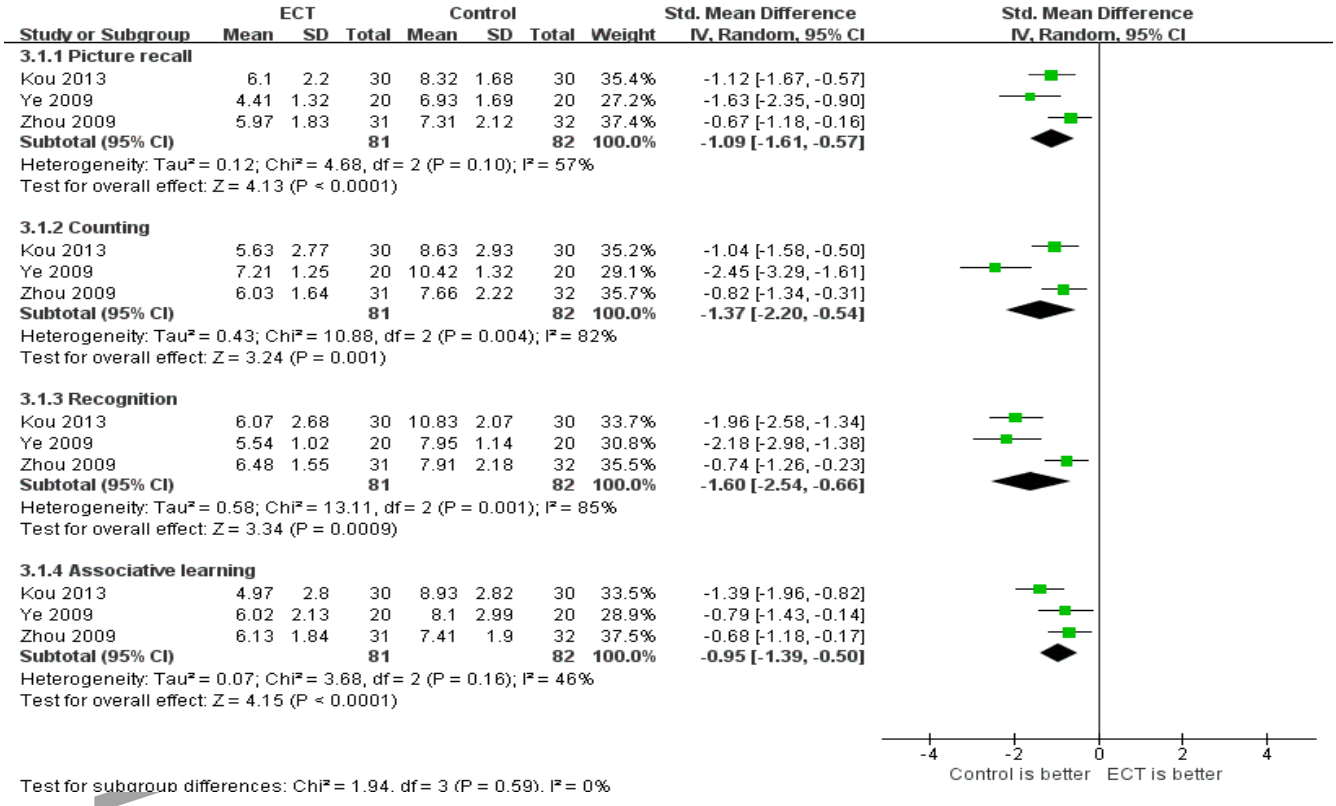
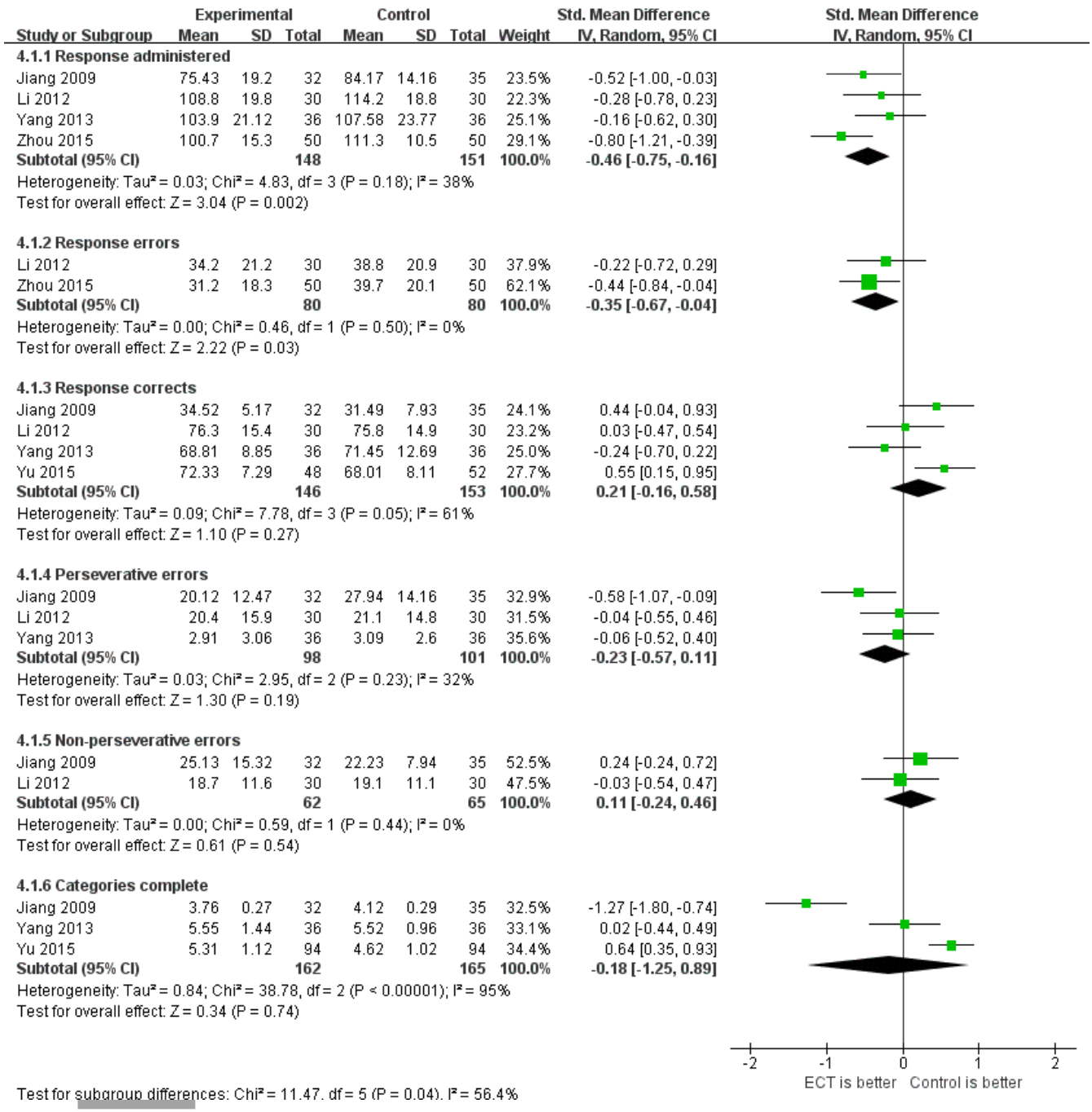


Figure 4 Electroconvulsive therapy (ECT)-related memory impairment in schizophrenia: forest plot for response administer, non-perseverative errors, perseverative corrects, perseverative errors, and categories complete assessed by Wisconsin Card Sorting Test at the end of ECT course


Experimental
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
4.1.1 Response administered
Jiang 2009 75.43 19.2 32 84.17 14.16 35 23.5% -0.52 [-1.00, -0.03]
Li 2012 108.8 19.8 30 114.2 18.8 30 22.3% -0.28 [-0.78, 0.23]
Yang 2013 103.9 21.12 36 107.58 23.77 36 25.1% -0.16 [-0.62, 0.30]
Zhou 2015 100.7 15.3 50 111.3 10.5 50 29.1% -0.80 [-1.21, -0.39]
Subtotal (95% CI) 148 151 100.0% -0.46 [-0.75, -0.16]
Heterogeneity: Tau² = 0.03; Chi² = 4.83, df = 3 (P = 0.18); I² = 38%
Test for overall effect: Z = 3.04 (P = 0.002)
4.1.2 Response errors
Li 2012 34.2 21.2 30 38.8 20.9 30 37.9% -0.22 [-0.72, 0.29]
Zhou 2015 31.2 18.3 50 39.7 20.1 50 62.1% -0.44 [-0.84, -0.04]
Subtotal (95% CI) 80 80 100.0% -0.35 [-0.67, -0.04]
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.22 (P = 0.03)
4.1.3 Response corrects
Jiang 2009 34.52 5.17 32 31.49 7.93 35 24.1% 0.44 [-0.04, 0.93]
Li 2012 76.3 15.4 30 75.8 14.9 30 23.2% 0.03 [-0.47, 0.54]
Yang 2013 68.81 8.85 36 71.45 12.69 36 25.0% -0.24 [-0.70, 0.22]
Yu 2015 72.33 7.29 48 68.01 8.11 52 27.7% 0.55 [0.15, 0.95]
Subtotal (95% CI) 146 153 100.0% 0.21 [-0.16, 0.58]
Heterogeneity: Tau² = 0.09; Chi² = 7.78, df = 3 (P = 0.05); I² = 61%
Test for overall effect: Z = 1.10 (P = 0.27)
4.1.4 Perseverative errors
Jiang 2009 20.12 12.47 32 27.94 14.16 35 32.9% -0.58 [-1.07, -0.09]
Li 2012 20.4 15.9 30 21.1 14.8 30 31.5% -0.04 [-0.55, 0.46]
Yang 2013 2.91 3.06 36 3.09 2.6 36 35.6% -0.06 [-0.52, 0.40]
Subtotal (95% CI) 98 101 100.0% -0.23 [-0.57, 0.11]
Heterogeneity: Tau² = 0.03; Chi² = 2.95, df = 2 (P = 0.23); I² = 32%
Test for overall effect: Z = 1.30 (P = 0.19)
4.1.5 Non-perseverative errors
Jiang 2009 25.13 15.32 32 22.23 7.94 35 52.5% 0.24 [-0.24, 0.72]
Li 2012 18.7 11.6 30 19.1 11.1 30 47.5% -0.03 [-0.54, 0.47]
Subtotal (95% CI) 62 65 100.0% 0.11 [-0.24, 0.46]
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)
4.1.6 Categories complete
Jiang 2009 3.76 0.27 32 4.12 0.29 35 32.5% -1.27 [-1.80, -0.74]
Yang 2013 5.55 1.44 36 5.52 0.96 36 33.1% 0.02 [-0.44, 0.49]
Yu 2015 5.31 1.12 94 4.62 1.02 94 34.4% 0.64 [0.35, 0.93]
Subtotal (95% CI) 162 165 100.0% -0.18 [-1.25, 0.89]
Heterogeneity: Tau² = 0.84; Chi² = 38.78, df = 2 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.34 (P = 0.74)
Test for subgroup differences: Chi² = 11.47, df = 5 (P = 0.04), I² = 56.4%
-2
-1
0
1
2
ECT is better
Control is better