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- Title: A SYSTEMATIC REVIEW ON COGNITIVE EFFECTS OF ELECTROCONVULSIVE THERAPY IN ASIAN PATIENTS
- Running Title: REVIEW ON COGNITIVE EFFECTS OF ECT IN ASIANS
- Article Type: Review Article
- KeyWords: Electroconvulsive therapy (ECT), cognition, cognitive impairment, psychiatric disorder, review, Asia

Abstract

Objective: Electroconvulsive Therapy (ECT) is the most efficacious treatment for many major mental illnesses but is limited by cognitive side effects. However, research on the pattern and severity of ECT-related cognitive side effects is inconsistent. Furthermore, little is known about the cognitive effects of ECT in Asian populations. A systematic review was conducted to examine objective cognitive performance following ECT in the Asian context.

Methods: This review systematically identified studies assessing ECT-related cognitive effects in PubMED, PsychINFO, The Cochrane Library, Journal of ECT and major databases in Asian countries. The search included publications from peer-reviewed journals of languages other than English.

Results: A total of 6,322 studies were identified; 823 were assessed for eligibility, of which 16 studies met the search criteria and were included in this review. Majority used high dose Bitemporal ECT for Depression and/or Schizophrenia. Cognitive impairment, which could occur immediate to the first ECT session, was reported in only 9 out of the 16 studies. However, deficits were observed to resolve as early as 3 weeks after the initiation of ECT. The remaining studies reported no impairment or even improvement after ECT.

Conclusions: There is no consistent evidence that suggests ECT causes cognitive deficits in patients, despite the widespread use of high dose Bitemporal ECT. This review suggests that Asian patients, presenting with a different psychiatric profile, may respond to high-dose Bitemporal ECT differently from Western samples.

Keywords: Electroconvulsive therapy (ECT), cognition, cognitive impairment, psychiatric disorder, review, Asia.

Introduction

Electroconvulsive Therapy (ECT) is used to treat a variety of mental disorders since its first successful treatment in 1938.[1] The efficacy of ECT has been well established, however, there remains a lack of clear consensus as to the potential risks involved.

ECT remains controversial mainly because some patients experience cognitive side effects. Transient postictal disorientation is well documented [2,3] but current literature regarding other cognitive effects of the procedure is inconsistent. The presence, severity and persistence of cognitive impairment after ECT may be attributable to differing techniques of administering ECT such as electrode placement, electrical waveform and electrical dosing. [4,5] A better understanding of the cognitive consequences of ECT could lead to increased acceptability of the procedure.

In a 2010 meta-analysis, Semkovska and McLoughlin examined transient (0 to 3 days), short-term (4 to 14 days) and long-term (14 days to 2 years) cognitive effects following ECT.[6] Existing research suggests impairment of executive functioning, processing speed, and anterograde memory in the first 3 days of ECT treatment. All of which demonstrated improvement beyond baseline levels after 15 days post-treatment. Ingram et al. reviewed selected research pertaining to the cognitive side-effects of specifically brief pulse ECT and similarly concluded that there was substantial evidence of a brief period of disorientation and memory impairment immediately after treatment.[7] Recovery can take place weeks and months after treatment completion. Relatively few studies have

examined non-memory cognitive functions and those that did showed mixed findings. Interestingly, the 2010 meta-analysis identified no effect of electrode placement or stimulus waveform on cognitive outcomes. Other short-term cognitive side-effects included subjective reports of memory problems. However, subjective impairment was found to correlate poorly with objective impairment, possibly due to the choice of assessment questionnaire and interviewer factors.[8] Notable long-term cognitive side-effects include retrograde amnesia (for both episodic and semantic memory), which was reported to persist for at least a year.

Not only is current literature limited by inconsistencies in methodologies and findings, there are also significant publication and selection biases in that these studies were conducted among samples from Western populations who were mostly diagnosed with Depression and published in English. There is a need to evaluate the evidence specific to Asian populations, since the practice of ECT in Asia is probably different from the West, for example in terms of technique and patient selection.

We found a systematic review and meta-analysis of studies published in both English and Chinese regarding the safety and efficacy of ECT combined with antipsychotic medication for treatment-refractory schizophrenia by Wang et al., reporting higher rates of memory impairment in the combined treatment group.[9] 2 of the included studies were from non-Asian samples but many of the included studies did not contain information about ECT technique. Hence, this systematic review is the first that we know of to look at

objective cognitive performance following ECT specifically in Asian populations across multiple psychiatric conditions in studies published in other languages.

Methods

Search Strategy

We searched the following databases and search engines for studies published from January 1980 to December 2017: PubMED, PsychINFO, The Cochrane Library, Journal of ECT, Indian Science Abstracts, Indian Journal of Psychiatry, CiiNi, Seishin Shinkeigaku Zasshi, Chulalongkorn University Library and Information Network. Three online Chinese periodical full text databases: CNKI, WANFANG DATA, VIP were adopted to review publications from China. We used the search terms 'ECT', 'electroconvulsive therapy', 'electroshock' & 'cognition', 'cognitive impairment', 'cognitive side-effect, 'asia', and the Chinese equivalent '无抽搐电休克疗法', '电击疗法', '认知功能', '认知缺损', '精神障碍患者', '亚洲' in the searches. Various combinations of these keywords were used to search for articles. Reference lists from review studies and related articles were also checked to search for relevant studies.

Inclusion and Exclusion Criteria

Our inclusion criteria were:

1. Studies published from 1980 to 2017.

2. Sample size of more than 5 human subjects, with no age restriction.
3. Clear psychiatric diagnoses must be present.
4. ECT technique must be stated, minimally electrode placement.
5. Objective cognitive data collected and compared at 2 or more time points.
6. Studies conducted in Asian populations i.e., including but not limited to India, China, Japan, Korea, Thailand, Singapore, Malaysia.
7. Studies published in any language.

Our exclusion criteria were:

1. Case studies, neuroimaging studies, animal studies, review studies and duplicated reports.
2. Studies that did not specify ECT technique.
3. Studies that measured only subjective cognitive impairment.
4. No mention of comparison of serial cognitive assessments.

Screening of Studies

All search results were imported into Endnote X6 software. Both authors independently screened titles and abstracts after removing the duplicates. The full texts of the remaining articles were screened according to the above-mentioned inclusion and exclusion criteria. When both parties could not decide upon the inclusion of a study, a third person made the

final determination. Figure 1 illustrates the selection process the authors undertook for this systematic review.

The data search by keywords generated 6,322 studies. 823 potentially eligible studies were identified after the removal of duplicates. Following which, 807 studies were excluded resulting in a total of 16 studies meeting all the inclusion criteria with 7 studies published in English and 9 in Chinese.

Results

16 studies were included in the final analysis. Notably, there were 6 studies that appeared to be potentially useful, but the full-text publications could not be obtained even after sourcing for channels to purchase the articles and attempting to contact the relevant authors through emails. These 6 studies were regrettably excluded from the final analysis (refer to Appendix in Supporting Document). Only 1 of these studies was not published in English or Chinese (Japanese).

We organized the 16 studies based on the language of publication and in chronological order (refer to Tables 1 and 2) and discuss them by the conclusions drawn.

Publications reporting no adverse cognitive side-effects (7 studies)

In a double-blind controlled study by Bagadia et al.,[10] 20 depressed and 20 schizophrenic patients were assigned to either Bitemporal ECT at fixed dose with placebo or simulated ECT with Imipramine (for patients with Depression) or Chlorpromazine (for patients with Schizophrenia) and assessed prior to first ECT session and 48 hours after the last session. Cognitive test scores did not show statistically significant changes pre- and post-ECT in both groups. Nevertheless, 20% of schizophrenic patients and 10% of depressed patients reported having subjective difficulty recalling material learned in past few days.

120 patients in a non-randomized, single-blind study by Chatterjee and Mohammed received either non-dominant hemisphere Unilateral ECT, dominant hemisphere Unilateral ECT or Bitemporal ECT at fixed dose and were assessed pre-ECT and 3 weeks after treatment completion.[11] Within-group comparison showed significant overall cognitive improvement for the Unilateral non-dominant hemisphere group (Schizophrenia $p<0.05$; Depression $p<0.05$), but no significant changes for the other two treatment groups. Whereas between-group comparisons showed no significant difference in overall memory score change except for improvement in tests of immediate auditory verbal recall ($p<0.05$) and memory dependent learning ($p<0.05$) only for the Unilateral non-dominant hemisphere group. This early Asian study was likely underpowered to detect a true association between ECT electrode placement and cognitive side-effects, regardless of psychiatric diagnosis.

Li et al. investigated the effect of Bitemporal ECT with age-based dosing on 60 Treatment-Resistant Depression patients by assessing them before ECT and the morning after the last session.[12] All tests assessing working memory, recall, speed of processing, frontal/executive function showed significant improvement (all $p<0.01$) except for Trail Making Tests A and B (executive function and processing speed). A similar study by Prakash et al. also using the Trail Making Tests on 40 patients with either Depression or non-affective psychosis who underwent brief pulse Bitemporal ECT with unknown dosing, however showed improvement at 4 weeks after treatment completion (TMT A and B $p<0.05$).[13]

In an observational study by Tan et al., Bitemporal ECT of unknown dosing was performed on 19 depressed patients and cognition was assessed before the initiation of ECT, 24 hours after first session and 24 hours after last session.[14] The increase in Memory Quotient (MQ) scores across the three time points did not reach statistical significance (75.16 ± 9.90 vs 78.05 ± 9.16 vs 77.94 ± 12.13, $F=1.329$, $p=0.278$). However, scores in block design 24 hours after first session ($p=0.004$) and associative learning 24 hours after last session ($p=0.012$) had significantly improved.

Tor et al. retrospectively analyzed data of 48 schizophrenia patients from sequential naturalistic cohorts between December 2014 and May 2016.[15] Based on the default treatment protocol at the time of treatment, patients underwent one out of four modalities: Bitemporal ECT with age-based dosing (BT-AB), Right unilateral ECT with stimulus

titration-based dosing (RU-ST), Bitemporal ECT with stimulus titration-based dosing (BT-ST) and Bifrontal ECT with stimulus titration-based dosing (BF-ST). General improvement was reported in total Montreal Cognitive Assessment (MoCA) scores for the whole study sample and for the BT-ST group ($p<0.05$), while no statistically significant difference was found across all four treatment modalities. Patients in the BT-AB group showed impairment in the delayed recall item of the MOCA ($p<0.05$). Due to the naturalistic nature of the study and its inherent rater bias, findings were limited in drawing conclusions between the treatment modalities, although the authors recommended that patients with poorer pre-treatment cognitive functioning avoid BT-AB.

Zhang et al. observed the effect of Bitemporal ECT with age-based dosing on executive functioning of 21 adolescent patients with schizophrenia in comparison with a group (n=22) treated with one atypical antipsychotic, using the Wisconsin Card Sorting Test (WCST) pre-ECT and 1 week after treatment completion.[16] The overall score ($p<0.05$) and score for perseverative errors ($p<0.05$) improved significantly for the ECT group, reflecting an improvement in patients' executive functioning in parallel with greater and faster resolution of psychotic symptoms.

These studies which included patients with Depression and Schizophrenia showed that there was no observed adverse effect on cognition, except for possible amnesic effects after BT-AB, as reported by Tor and colleagues.[15] However, this finding was not seen in

the other studies using similar electrode placement and dosing strategy. Interestingly, non-memory cognition improved in 5 of the studies, with 1 paper [11] suggesting that unilateral electrode placement may have an advantageous effect. However, the strength of the findings is limited by the fact that they are either observational studies or low-quality clinical trials with inadequate randomization and/or blinding.

Publications reporting transient cognitive side-effects (4 studies)

Guo et al. examined the effect of Bitemporal ECT with unknown dosing strategy on 49 Depression patients by assessing them with the California Verbal Learning Test (CVLT) and the Wechsler Memory Scale (WMS) prior to the start of ECT, and weekly during the 3-week treatment.[17] They reported a decline in performance in all domains of CVLT and WMS in the first week. After 2 weeks of treatment, all areas of performance except free recall and short-term free recall returned to baseline. After 3 weeks of ECT, the CVLT and WMS scores were higher than at enrolment (all $p<0.05$).

45 patients with Major Depression were treated with Bitemporal ECT with age-based dosing and their cognitive performance was evaluated by Lou et al. before initiation, the day after the first session and the second day after treatment completion.[18] After the first session, patients performed significantly worse for the Associate Learning, Figural Memory (ps<0.05), Logical Memory and Digit Span (ps<0.01) subtests in WMS but after treatment completion, their scores recovered to baseline ($p<0.05$).

In a randomized clinical study by Song et al., 100 depressed patients were either treated with Bitemporal ECT or Unilateral ECT of non-dominant hemisphere with age-based dosing.[19] It was observed that 1 day after completion of ECT, while no cognitive changes occurred for Unilateral ECT, some cognitive abilities (visual memory, auditory memory, and spatial ability) were temporarily compromised ($ps < 0.05$) for those who received Bitemporal ECT. Two weeks after treatment completion, both groups surpassed their baseline scores in all domains tested, suggesting that Bitemporal ECT has a more adverse albeit transient effect on overall cognition than Unilateral ECT.

Similarly, Zhou et al. described a randomized controlled trial of Bitemporal ECT with age-based dosing plus Olanzapine versus Olanzapine only in 63 treatment-resistant schizophrenia patients.[20] Scores from 4 subtests of the WMS declined significantly for the ECT group at 2 weeks after treatment initiation, with a nadir at 4 weeks, recovering to baseline at 8 weeks and improving significantly from baseline at 12 weeks after initiation of treatment (eg, Figural Memory $p<0.01$). The control group instead showed gradual improvement surpassing baseline at 12 weeks after treatment initiation ($p<0.01$), and no significant difference from the ECT group at final study assessment ($p=0.48$).

These 4 studies demonstrated that Bitemporal ECT with age-based dosing can be associated with transient cognitive impairment early during treatment, but appears to resolve by the end of treatment, with perhaps even improved scores at approximately 4 weeks after the completion of treatment. Unilateral ECT does not appear to have such an

effect on cognitive function. Once again, the conclusions are limited by the high risk of selection and rater biases in these under-powered low-quality randomized trials, also by the lack of standardization in the methods and timing of cognitive testing.

Publications reporting short-term cognitive side-effects (5 studies)

In a study by Bagadia et al., 20 schizophrenic patients were each treated with Bitemporal ECT or Right Unilateral ECT at fixed dose in a double-blind randomized trial.[21] While learning was reported to have improved after 6 ECT sessions for 8 patients each in both groups, 8 Bitemporal ECT patients and 6 other Right Unilateral ECT patients performed worse. Similarly, for unaided recall, improvement was seen in 9 patients each in both groups and worsened in 3 Bitemporal ECT and 5 Right Unilateral ECT patients. The authors had failed to report the mean cognitive scores nor analyzed the effect size at each assessed time-point. We were thus unable to interpret the data meaningfully.

Fujita et al. analyzed data from a retrospective naturalistic cohort of patients.[22] Patients admitted before February 2004 received Bitemporal sine wave ECT at fixed dose while those admitted after received Bitemporal pulse wave ECT at age-based dosing. There were 9 patients in each treatment group that were assessed cognitively 3-14 days before treatment initiation and 3-14 days after treatment completion. Both groups did not show significant change in MMSE and WMS scores in both within-group and between-group comparisons. However, there was significant improvement in post-treatment visual

memory (p=0.02), general memory (p=0.01) and divided attention (p=0.001) within the pulse wave group. On the other hand, those who received sine wave ECT displayed significantly poorer performance in Stroop test (p=0.02) and Dual Task (p=0.01), both tests of attention. Between-group comparisons revealed superiority of pulse wave over sine wave in terms of the dual task (p = 0.004). The authors acknowledged the limitation of its small sample size but suggested that sine wave Bitemporal ECT was associated with impairment of executive function even though overall ECT did not appear to have an effect on memory.

Kunigiri et al. studied 15 patients with major depressive disorder, 10 of whom received Bitemporal ECT and 5 of whom received Right Unilateral ECT, all at suprathreshold dosing.[23] A neurocognitive battery measured orientation within 48 hours before first session and at 20 minutes, 50 minutes, 2 hours and 8 hours after the second and fifth ECT session, and retrograde and anterograde memory within 48 hours before the first ECT and 8 hours after the second and the fifth session. Disorientation (all ps < 0.001) and memory impairment (all verbal tests' ps < 0.001, except p = 0.03 for Benton visual retention test) occurred with cumulative effects. Subgroup analysis of the different ECT techniques was not performed.

55 patients with major depression underwent 6 Right Unilateral ECT sessions at seizure threshold dosing in a study conducted by Wang and colleagues.[24] The findings revealed significantly poorer orientation scores (p < 0.001), autobiographical memory (p = 0.003)

but faster reaction time ($p < 0.001$) 2 days after completion of 6 Right Unilateral ECT sessions. Associative learning was better after ECT ($p = 0.006$).

Tao and Huang looked at the effect of Bitemporal ECT on cognitive functioning in a randomized controlled trial of 180 patients diagnosed with schizophrenia, depression, or mania.[25] 90 patients received pharmacotherapy while the remaining 90 received Bitemporal ECT with age-based dosing. WMS, WCST and Continuous Performance Task (CPT) were administered to compare cognitive capacities of these patients and both treatment groups showed deficits in memory, attention and executive functioning at 28 days after treatment completion with the ECT group performing significantly worse than the pharmacotherapy group (between group comparison at 28 days post-treatment: WMS Overall score $p<0.001$, WCST category score $p<0.001$, CPT3 $p=0.034$) .

From these 5 studies, short-term cognitive side-effects were observed after the fifth ECT session, lasting up to 28 days after completion of the treatment course, and even in patients receiving unilateral ECT but at suprathreshold dose.

ECT-related cognitive effects in patients with depression and schizophrenia

Of the 16 studies, 9 examined patients diagnosed with depression, 4 examined patients with schizophrenia, while samples in the remaining 3 studies consisted of patients with both disorders.

6 studies with depressed patients indicated greater cognitive deficits (i.e., memory, attention, learning) with the usage of Bitemporal and Bilateral ECT, although the deficits generally returned to baseline after 3 weeks. [17-19,22-24] Similar side-effects, lasting 28 days after treatment, were identified in Tao and Huang's study sample with depressed and schizophrenic patients. [25]

Short-term memory and learning impairment were noted in 2 studies examining schizophrenic patients. While Zhou et al. reported improvement in memory 8 weeks after treatment course, cognitive performance was not assessed beyond the sixth ECT session in Bagadia et al. [20-21]

Discussion

In Western countries, ECT is mostly performed on middle-aged women with Depression, whereas the usual ECT patient profile in Asia is a young man diagnosed with schizophrenia.[26-28] Disparities in ECT technique exist even between Asian countries. For instance, sine wave ECT devices were used in 2 out of 12 Asia-Pacific countries surveyed while brief-pulse devices were utilized in the others. All surveyed countries used bilateral electrode placement and reported memory deficits as the most common side-effect.[27] Although ECT is commonly practiced in Asia, research on its impact on cognition is sparse. Hence, we believed that it was important to review the literature specifically from the region that studied samples of patients with other psychiatric

conditions and may be published in other languages. Indeed, our search revealed studies published in English, Chinese and Japanese.

Findings from this review are inconsistent. Majority of the studies used Bitemporal ECT at either fixed dose or age-based dosing, and nearly half of the studies found no adverse ECT-related cognitive side-effects and some even showed significant improvement in patients' memory and non-memory cognitive functions by the end of the treatment. 4 out of the 16 papers found that ECT is associated with significant cognitive impairment mostly evident within the first few sessions of ECT. However, deficits tended to resolve, and end-point cognition was comparable to or even improved from baseline performance. Significant cognitive deficits owing to ECT persisting up to 4 weeks after treatment completion was reported in the remaining 5 papers, even when Right Unilateral ECT at threshold or suprathreshold doses was used. These studies reported an adverse effect on orientation, executive functions, attention, memory and autobiographical memory. Our findings partially resonate with the conclusions drawn in Semkovska and McLoughlin's systematic review.[6]

The main strength of this review is the inclusion of a large proportion of patients with non-depressive psychiatric illness in Asian populations by intentionally including studies published in other languages. Significant heterogeneity of the study samples with some studies including both Depression and Schizophrenia without subgroup analysis, although representative of real-world practice, may have contributed to the lack of conclusive

findings. Contrary to earlier research [4,5,6] performed on the topic which suggested that higher electrical doses were associated with more cognitive impairment, almost half of our reviewed studies did not report this effect despite using fixed dosing or age-based dosing strategies which typically apply higher doses than stimulus titration strategies. Out of 5 studies reporting the use of Unilateral ECT, 3 of them [21,23,24] reported deficits in orientation and memory in the short-term after completion of a course of ECT even when 1 of these [24] applied a dose at seizure threshold. Findings on non-memory cognitive functions were similarly inconsistent, from no impairment (even perhaps improvement) to transient impairment to short-term impairment. In the study by Wang et al., there was both decline in orientation and autobiographical memory and improvement in reaction time and learning.[24] This suggests that Asian populations may demonstrate a different side-effect profile to different ECT techniques or possess hitherto unreported and unstudied risk factors associated with cognitive impairment after ECT.

This systematic review is not without its limitations. Only full-text studies in English and Chinese were found. Studies from other regions in the Asian continent that were published in other languages could not be included and assessed accordingly. For the 16 selected articles, the English studies were of a higher methodological quality and had better-reported details of the ECT protocol. Nevertheless, using the framework of Grading of Recommendations, Assessment, Development and Evaluations (GRADE), all the studies were rated low to very low in quality of evidence, as the included studies were either of retrospective cohorts and under-powered observational studies or low-quality trials with inadequate randomization and blinding and lack of power calculation.

Another constraint of our systematic review is the lack of studies that addressed the long-term effect of ECT on cognition. None of the 16 papers assessed cognition beyond 2 months when the recommended duration of study is 6 months or longer.[29] In addition, the possible confounding effect of the psychiatric illness itself and concurrent medications were not specifically controlled for most of the studies.

Our review reinforces several important issues for future research. Appropriately designed and adequately powered clinical trials with standardized outcome measures and assessment schedules are needed to better define the pattern, spectrum, as well as risk factors for ECT-induced cognitive impairment. Beyond some possible initial decline, followed by subsequent recovery, this review did not provide conclusive evidence that suggests ECT causes persistent cognitive deficits in patients. Still, uncertainties remain on the demographic, clinical and procedural risk factors associated with the occurrence of ECT-related cognitive side-effects in the Asian population.

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Appendix

List of potential studies that were excluded from study

Table 1. Studies Excluded from Systematic Review

Author(s)	Year	Country	Title
Motohashi, N., Takano, H., Terada, T. et al.	2000	Japan	Preliminary report on the efficacy and safety of brief-pulse ECT in depression. (Article written in Japanese)
Chanpattana, W.	2000	Thailand	Maintenance ECT in treatment-resistant schizophrenia. (Full-text article not accessible)
Chanpattana, W.	1998	Thailand	Maintenance ECT in schizophrenia: a pilot study. (Full-text article not accessible)
Chanpattana, W.	1997	Thailand	Continuation electroconvulsive therapy in schizophrenia: a pilot study. (Full-text article not accessible)
阚博	2014	China	无抽搐电休克治疗对精神分裂症患者前瞻性记忆功能影响的研究 (Full-text article not accessible)
林泽涯，许国安，吕耀明	1997	China	精神病患者 ECT 前后 EEG, WMS 检测结果分析 (Full-text article not accessible)

Table 1. Studies Published in Chinese Included For Systematic Review

Author/ Country	Methodology	Subject Characteristics	Indication for ECT	ECT Technique	Cognitive Measurements	Assessment Schedule	Cognitive outcome	Risk of bias	GRADE rating
1. Wang et al (2003) / China	Observational	N=55, age range 18-50, mean 24.9 (8.6) years	Major Depression	Right unilateral, treatment dose at seizure threshold, pulse-width unknown, 3 times weekly for total 6 sessions	1. Memory battery consisting of tests of orientation, autobiographical memory, associative memory 2. test of reaction time	1. Pre-ECT 2. 2 days after treatment completion	Significant decline in orientation score (15.81 ± 7.58 vs 13.56 ± 5.97) and autobiographical memory (13.78 ± 8.78 vs 11.41 ± 6.69). Significant improvement in associative memory (17.38 ± 7.96 vs 19.56 ± 6.17) and reaction time (860.16 ±256.63 vs 679.97 ± 176.00)	High (no controls)	Very Low
2. Tan et al (2004) / China	Observational	N=19, age range 15-49, mean 31.2 (8.6) years	Major Depression	Bitemporal, dosing unknown, pulse-width unknown, average 4 sessions in total	1. Locally adapted Wechsler Memory Scale-Revised, 2. Block Design, 3. Fourth Exception Test (a locally developed and validated test for abstract thinking)	1. Pre-ECT 2. 24 hours after first session 3. 24 hours after treatment completion	No significant change in cognitive scores overall except Block Design (30.47 ± 5.58 vs 33.68 ±6.90 24 hours after first session), and Associate Learning (13.26 ±4.45 vs 17.14 ± 4.46 after treatment completion) improved significantly	High (no controls)	Very Low
3. Zhou et al. (2009) / China	Randomized controlled trial of ECT + Olanzapine vs Olanzapine only	N=31 in ECT group (mean age 43.1 {9.1} years) and N=32 in Olanzapine group (mean age 42.2 {8.6} years)	Treatment-resistant schizophrenia	Bitemporal, age-based dosing, pulse-width unknown, 2 to 3 times weekly for a total of 8 to 12 sessions	4 subtests from locally adapted Wechsler Memory Scale-Revised – Logical memory, Associate Learning, Figural Memory, Digit Span	2, 4, 8 and 12 weeks after the beginning of the course of ECT	Scores of all subtests declined at 2 weeks with a nadir at 4 weeks, but recovered to baseline at 8 weeks, and improved significantly from baseline at 12 weeks. (eg. Figural Memory 7.13 ± 2.06 vs 6.42 ± 1.98 vs 5.97 ± 1.83 vs 6.61 ±2.20 vs 7.68 ± 2.06) Control group showed gradual improvement with improvement from baseline at 12 weeks, (6.97 ± 2.25 vs 7.06 ±2.17 vs 7.31 ± 2.12 vs 7.81 ± 2.51 vs 8.13 ± 2.83) and no significant	High (randomization, allocation, rater-blinding not mentioned)	Low

								difference from treatment group at 12 weeks.		
4.	Song et al (2010) / China	Randomized trial of Bitemporal ECT vs Unilateral ECT of non-dominant hemisphere	N=100, age range 18-59 years	Major Depression	Bitemporal (n=50) and Unilateral (n=50), age-based dosing, pulse width unknown, alternate days for total 6 sessions	1. Locally adapted Wechsler Memory Scale-Revised 2. Fourth Exception Test 3. Locally adapted Block Design test	1. Pre-ECT 2. 1 day after treatment completion 3. 2 weeks after treatment completion	For Bitemporal group, scores in Visual Reproduction (7.34 ± 2.82 vs 6.23 ± 2.45 vs 8.45 ± 2.37), Associate Learning (8.92 ± 4.26 vs 7.23 ± 4.07 vs 10.42 ± 4.80) and Block Design (18.62 ± 4.85 vs 16.53 ± 4.50 vs 20.65 ± 4.96) declined significantly at first, then improved significantly from baseline at 2 weeks post-treatment. Unilateral group did not show such decline. Both groups showed significant improvement from baseline in all domains.	High (randomization, allocation, rater-blinding not mentioned)	Low
5.	Lou et al (2011) / China	Observational	N=45, age range 18-60 years, mean 32.9 (9.4) years	Major Depression	Bitemporal, age-based dosing, pulse width unknown, thrice weekly for total 6-8 sessions	4 subtests from locally adapted Wechsler Memory Scale-Revised – Logical memory, Associate Learning, Figural Memory, Digit Span	1. Pre-ECT 2. The day after the first session 3. The second day after treatment completion	All scores declined after the first session but recovered with no significant difference from baseline after treatment completion. Logical memory (9.34 ± 3.63 vs 7.25 ± 2.74 vs 9.73 ± 3.72) Associate Learning (8.72 ± 3.45 vs 7.16 ± 2.71 vs 9.79 ± 3.75) Figural Memory (7.18 ± 2.97 vs 5.93 ± 2.12 vs 8.47 ± 3.38) Digit Span (8.36 ± 3.27 vs 6.42 ± 3.06 vs 9.12 ± 3.71)	High (no controls)	Very Low
6.	Tao and Huang (2012) / China	Randomized controlled trial of Bitemporal ECT vs medication only	N=180, 90 in each group ECT group age range 17-48, mean 26.25 (5.78) years Medication group age range 16-45, mean 26.70 (6.54) years	Schizophrenia, Schizoaffective Disorder, Major Depression and Bipolar Disorder	Bitemporal, age-based dosing, pulse-width 1.0msec, daily for the first 3 days then alternate day for a total of 3-12 sessions, mean 5.8 (2.1) sessions,	1. Wechsler Memory Scale (WMS) 2. Wisconsin Card Sorting Test (WCST) 3. Continuous Performance Task (CPT)	1. Pre-ECT 2. 1, 14 and 28 days after treatment completion	Both groups showed significant decline in scores on all tests at 28 days after treatment. ECT group: WMS (92.08 ± 11.84 vs 87.41 ± 8.64) WCST (7.47 ± 0.88 vs 6.52 ± 0.69) CPT (9.44 ± 1.27 vs 7.47 ± 9.88) Scores for ECT group significantly worse than	High (randomization, allocation, rater-blinding not mentioned)	Low

					56 subjects had fewer than 6 sessions, 34 subjects had more than 6 sessions			medication group at 28 days after treatment Medication group: WMS (93.92 ± 9.91 vs 92.90 ± 9.91) WCST (7.56 ± 0.74 vs 7.38 ± 0.66) CPT (10.20 ± 1.44 vs 9.91 ± 1.24)		
7.	Guo et al (2013) / China	Observational	N=49, age range 16-49 years, mean age 34.0 (12.0) years	Major Depression	Bitemporal, dosing unknown, pulse-width unknown, 3 times weekly for 3 weeks, total 9 sessions	1. California Verbal Learning Test (CVLT) 2. WMS	After the first, second and third week of treatment	All scores significantly declined after first week of treatment, then recovered to significantly better than baseline after treatment completion. CVLT free recall overall score (55.41 ± 3.68 vs 42.32 ± 2.94 vs 50.22 ± 3.27 vs 65.21 ± 3.49) WMS Memory Quotient (92.45 ± 19.75 vs 78.68 ± 14.69 vs 89.84 ± 16.72 vs 95.92 ± 16.84)	High (no controls)	Very Low
8.	Zhang et al (2014) / China	Observational comparison of a cohort of ECT adolescent patients vs a cohort of adolescent patients on one atypical antipsychotic	N=21 in ECT group, age range 13-18 years, mean age 16.1 (1.9) years. N=22 in control group, age range 13-18 years, mean age 15.6 (1.7) years	Schizophrenia	Bitemporal, age-based dosing, pulse-width unknown, 3 times weekly for a total of 8 sessions	WCST	Pre-ECT and 1 week after treatment completion	Overall score and score for perseverative errors improved significantly post-ECT for ECT group, whereas the scores for the control group did not change significantly. Overall score (92.23 ± 21.12 vs 78.95 ± 20.2) Perseverative error score (35.63 ± 15.46 vs 21.31 ± 11.87)	High (non-randomized, non-blinded)	Very Low
9.	Li et al (2015) / China	Observational	N=60, age range 25-45 years, mean age 34.0 (10.1) years	Treatment-resistant Depression	Bitemporal, age-based dosing, pulse-width unknown, total 8 sessions completed within 3 weeks with 1-2 days between sessions	1. WCST 2. Tower of Hanoi 3. Verbal Fluency 4. Digit Span 5. Digit Symbol 6. Visual Reproduction 7. Trail Making Tests A and B (TMT)	Pre-ECT and the morning after last session of ECT	All scores showed significant improvement except for TMT. WCST Error score (21.23 ± 10.16 vs 17.22 ± 10.40) Tower of Hanoi Overall Score (28.15 ± 17.63 vs 35.93 ± 16.83) Verbal Fluency (11.15 ± 3.99 vs 13.18 ± 4.28) Digit Span (9.95 ± 2.55 vs 11.33 ± 2.01) Digit Symbol (30.77 ± 9.12 vs 33.32 ± 8.27)	High (no controls)	Very Low

		Visual Reproduction (7.10 ± 3.15 vs 8.47 ± 3.23) TMT A completion time (53.24 ± 16.58 vs 52.61 ± 20.07 TMT B completion time (92.38 ± 39.67 vs 90.86 ± 18.63)

Table 2. Studies Published in English Included For Systematic Review

	Author/ Country	Methodology	Subject Character-istics	Indication for ECT	ECT Technique	Cognitive Measurements	Assessment Schedule	Cognitive outcome	Risk of bias	GRADE rating
1.	Chatterjee et al (1980) / India	Non-randomized, single-blind trial	N=120, age range 16-50 years	10 Major Depression, 30 Schizophrenia in each treatment group	1. Bitemporal 2. Unilateral non-dominant hemisphere 3. Unilateral dominant hemisphere Fixed dose, unknown pulse-width	7 subtests from Indian version of Boston Memory Scale 1. Digit forward 2. Digit backward 3. Personal data (remote) 4. Personal data (recent 5. Common knowledge 6. Counting 20 to 1 7. Paired associates	1.Pre-ECT 2.3 weeks after treatment completion	Within-group comparison showed significant improvement for group 2 only. Schizophrenia memory score Δ 6.57 SD 13.44 Depression mean memory score Δ 4.50 SD 5.66 Between-group comparison showed no significant difference overall. Between-group comparison showed significant improvement in immediate auditory verbal recall (mean Δ +0.88 SD 1.88) and memory dependent learning (mean Δ +2.19 SD 5.46) for group 2.	High (non-randomized, rater-bias)	Low
2.	Bagadia et al (1981) / India	Double-blind controlled	N=40, age range 18-65 years	20 Depression, 20 Schizophrenia	1. Bitemporal with placebo, fixed dose, pulse-width unknown (n=20, 10 depressed and 12 schizophrenic) 2. simulated ECT with imipramine for Depression or chlorpromazine for Schizophrenia (n=20, 10 depressed and 8 schizophrenic)	1. Koh's Block Design Test 2. Picture Recognition Test 3. B.G Test 4. Arithmetic 5. Immediate memory (digits) 6. Sentence Repetition 7. remote memory 8, recent memory	1. Pre-ECT 2. 48 hours after treatment completion	No significant change in cognitive test scores in both groups. Significant improvement in Koh's Block Design Test regardless of ECT when analysed by diagnosis group. Depression: ECT with placebo Mean percent change +52.22 SD 50.39, $p<0.01$ Depression: simulated ECT with imipramine Mean percent change +44.08 SD 48.43, $p<0.05$ Schizophrenia: ECT with placebo Mean percent change +38.5 SD 33.2, $p<0.05$ Schizophrenia: simulated ECT with chlorpromazine Mean percent change +20.1 SD 15.8, $p<0.05$	High (not randomized)	Low

3.	Bagadia et al (1988) / India	Double-blind, randomized trial	N=40, age range 18-65 years	Schizophrenia	1. Bitemporal (n=20) 2. Right unilateral (n=20) Fixed dose, pulse-width unknown, first 3 sessions in 2-day intervals, next 3 at 4-day intervals	Specially developed cognitive battery to assess learning, unaided recall, recognition and confabulation	1. Pre-ECT 2. After 3 sessions 3. After 6 sessions	Specific score not reported. Authors reported memory improvement in 40% of sample and impairment in 30% of sample, similar rates in both treatment groups.	High (randomization, allocation, rater-blinding not mentioned)	Very Low
4.	Fujita et al (2006) / Japan	Retrospective naturalistic cohort	N=18, mean age 49.8 (9.9) years	Major Depression, Bipolar Disorder (I or II)	6-12 sessions of: 1. Bitemporal sine wave at fixed-dose with stepwise increments until seizure induced, mean of 9.9 (2.8) sessions 2. Bitemporal pulse-wave at aged-based dose with stepwise increments until seizure induced, mean of 11.0 (2.0) sessions	1. MMSE 2. WMS-Revised 3. TMT A and B 4. Stroop Test 5. Verbal and Letter Fluency 6. Digit Symbol 7. Dual task	1. 3-14 days pre-ECT 2. 3-14 days after treatment completion (mean 8.2 SD 3.5 days)	No significant change in pre- and post-ECT MMSE and WMS scores. Significant improvement in Visual memory (57.9 ± 5.0 vs 61.6 ± 5.1) and General Memory (113.7 ± 19.9 vs 127.7 ± 25.3) for the pulse wave group. Impaired attention/executive function for the sine wave ECT group, (errors on Stroop Test 0.9 ± 0.6 vs 2.3 ± 1.1 and Dual Task 88.5 ± 4.3 vs 78.9 ± 7.6). Attention/Executive function scores improved for the pulse-wave group, (Dual Task 77.2 ± 11.1 vs 88.2 ± 7.3). The between-group difference in Dual Task performance was significant.	High (no controls)	Very Low
5.	Kunigiri et al (2007) / India	Observational	N=15, mean age 31.6 (6.5) years	Major Depression with melancholia	1. Bitemporal (n=10) 2. Right unilateral (n=5) Suprathreshold dosing, pulse-width unknown, 3 times per week	1. Orientation Battery Test (OBT) 2. TMT A 3. Verbal Paired Associates from WMS 4. Verbal Learning Test 5. Passage Test 6. Benton Visual Retention Test	1. within 48 hours before first ECT 2. after 20 mins, 50 mins, 2 hours and 8 hours after the second and fifth sessions for the Orientation Battery Test and TMT 3. 8 hours after second and fifth sessions for memory tests	Orientation and TMT scores declined at 20 mins then recovered by 8 hours post-ECT. After second session: OBT - 12 (0.0) vs 6.6 (2.7) vs 9.6 (1.6) vs 10.8 (1.4) vs 11.8 (0.4) TMT – 66.8 (27.3) vs 139.6 (78.5) vs 92.2 (63.9) vs 63.9 (18.9) vs 61.9 (20.3) After fifth session: OBT - 12 (0.0) vs 4.9 (3.0) vs 9.3 (2.0) vs 10.3 (2.6) vs 11.7 (0.6) TMT – 66.8 (27.3) vs 135.1 (109.4) vs 98.1 (71.6) vs 74.8 (43.3) vs 60.8 (19.8) Significant decline in all memory scores Verbal Paired Associates	High (no controls)	Very Low

								9.1 (0.9) vs 5.9 (1.4) vs 5.3 (1.8) Verbal Learning 9.8 (1.0) vs 6.2 (2.6) vs 4.3 (1.6) Passage Test 14.9 (1.7) vs 15.7 (3.3) vs 9.6 (3.5) BVRT 8.8 (0.8) vs 8.3 (0.8) vs 7.7 (1.5)		
6.	Prakash et al (2015) / India	Observational	N=40, mean age 34.6 (3.7 years)	Depression, Non-affective psychotic disorders	Bitemporal, brief pulse, dosing and pulse-width unknown, twice weekly	TMT and B	1. Pre-ECT 2. after treatment completion 3. 4 weeks after treatment completion	Significant improvement by 4 weeks after ECT TMT A: 22.20 (3.63) vs 19.85 (2.91) vs 17.52 (3.23) TMT B: 50.75 (6.84) vs 46.62 (6.33) vs 45.95 (6.53)	High (no controls)	Very Low
7.	Tor et al (2017) / Singapore	Retrospective naturalistic cohort	n=48, mean age 43.74 (10.82) years	Schizophrenia	1. Bitemporal (n=17) age-based dosing, 0.5ms pulse-width, mean 9.5 (3.4) sessions 2. Right unilateral (n=10) stimulus titration, 0.5ms pulse-width, mean 8.0 (3.3) sessions 3. Bitemporal (n=10) stimulus titration, 0.5ms pulse-width mean 11.3 (1.9) sessions 4. Bifrontal (n=11) stimulus titration, 1.0ms pulse-width, mean 11.6 (3.8) sessions	Montreal Cognitive Assessment (MoCA) total score and score of delayed recall item	1. 1-2 days pre-ECT 2. 1-2 days after treatment completion	Group 1 showed significant decline in delayed recall. 1.88 (1.93) vs 0.59 (1.12) Group 3 showed significant improvement in total score. 16.3 (11.0) vs 24.0 (5.0) General significant overall improvement in total MoCA score with no significant between group differences. 16.8 (9.1) vs 20.7 (6.0)	High (no controls)	Very Low

Figure 1. Literature search process and the corresponding number of publications at each stage.