

• Original article •

Meta-analysis of studies in China about changes in P300 latency and amplitude that occur in patients with schizophrenia during treatment with antipsychotic medication

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Background: Studies using event-related potential (ERP) methods have reported a relationship between the cognitive dysfunction of patients with schizophrenia and P300 latency and amplitude, but it remains uncertain whether or not these indices change as cognitive functioning improves with pharmacological treatment.

Aim: Pool the results from follow-up studies conducted in China to determine the relationship of treatment with antipsychotic medication to changes in P300 indices.

Methods: Studies conducted in China and published in English or Chinese from January 1982 to December 2011 that reported P300 latency and amplitude in patients with schizophrenia before and after treatment with antipsychotic medications were identified by electronic and hand searches, and the 12 studies that met inclusion criteria for the meta-analysis were independently reviewed by two evaluators. The peak P300 amplitude results for the 17 samples reported in the 12 studies were homogenous so a fixed-effects model was used to assess pooled standardized effect size (PSES); but the results for P300 latency were heterogeneous so a random-effects model was used to compute PSES. Publication bias was assessed using Egger's test, Begg's test and funnel plots.

Results: Of the pooled sample of 611 participants, the 502 participants (82.2%) who completed P300 latency and amplitude measures both before and after treatment were included in the meta-analysis. We found that antipsychotic treatment is associated with a small but significant increase in the amplitude of P300 (PSES=0.39, 95% CI [0.26, 0.51], $z=6.14$, $p<0.001$) and a small but significant decrease in the latency of P300 (PSES= -0.29, 95% CI [-0.51, -0.07]; $z=2.58$; $p=0.010$). There was no significant publication bias in either of the results.

Conclusion: In contrast to meta-analysis from western countries — that are primarily based on cross-sectional studies — the current meta-analysis of follow-up treatment studies of schizophrenia in China found that P300 amplitude and latency both change with pharmacological treatment. These findings suggest that P300 indices, particularly P300 amplitude, could be valuable biomarkers to monitor changes in cognitive functioning during treatment of patients with schizophrenia.

1. Introduction

Patients with schizophrenia have moderate to severe cognitive impairment that is improved with antipsychotic medications.^[1] Several electrophysiological studies^[2] of schizophrenia using event-related potential (ERP) techniques report prolonged P300 latency and reduced P300 amplitude which appear related to cognitive functioning, so some authors have suggested that these indices should be used as biomarkers for the cognitive dysfunction associated with schizophrenia.^[3] However,

there remains controversy about whether or not the abnormalities in P300 resolve during treatment with antipsychotic medications. Some authors report no change in P300 latency and amplitude with antipsychotic treatment^[4,5], while other authors find that these indices return to normal with antipsychotic treatment.^[6,7] Most of these studies that compare P300 before and after antipsychotic treatment have small sample sizes and several of them have only been published in Chinese. Previous meta-analyses of P300 studies in schizophrenia^[2] are primarily based on cross-sectional

studies that do not assess changes in P300 indices with treatment. The current paper reports on a meta-analysis of studies conducted in China that assess changes in P300 in patients with schizophrenia before and after treatment with antipsychotic medication.

2. Methods

2.1 Study ascertainment

The results of the search strategy are shown in Figure 1. The following databases were used to identify potential studies for the meta-analysis: English-language papers were identified from PubMed, Web of Knowledge, EMBase, Cochrane Library, and PsycINFO; Chinese-language papers were identified from the Chinese Science and Technology Journal Database (CSTJ),^[8] Chinese Biomedical Literature Disc Database (CBM disk),^[9] Chinese National Knowledge Infrastructure (CNKI),^[10] and Wanfang Data.^[11] Papers published between 1 January 1982 and 31 December 2011 were considered. The search strategy was based on guidelines recommended by the Cochrane Collaboration.^[13] The keywords used in the search included English and Chinese versions of the following terms: P300, sensory gating, schizophrenia, schizophrenic, psychosis, China, Chinese, Han and truncation operators of the English-language terms. We also conducted a manual search of articles published over the last six months in key journals in China (the Chinese Journal of Psychiatry, the Chinese Medical Journal, the Chinese Mental Health Journal, the Chinese Journal of Nervous and Mental Disorders, and the Shanghai Archives of Psychiatry) and of articles listed in the reference of the papers that were identified by the electronic search. As shown in Figure 1, 309 papers were identified using this electronic search strategy and an

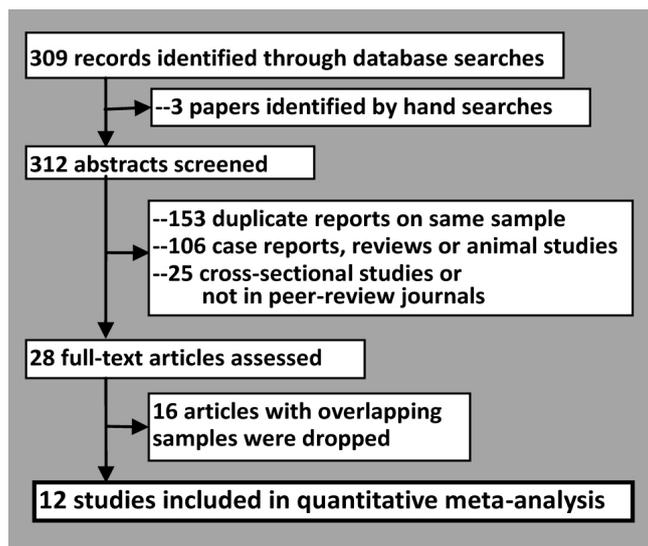
additional 3 papers were identified by hand-searching.

These 312 abstracts were independently assessed by two reviewers (the first and second author) to determine whether or not it was necessary to assess the full-text article. After excluding 284 papers because they were secondary reports of previously published data sets, case reports, cross-sectional studies, animal studies, reviews, or articles that were not from peer-review journals, 28 potential articles remained. Based on meta-analysis guidelines recommended by the Cochrane Collaboration,^[13] the full text of these 28 articles were independently evaluated by the two reviewers to determine whether or not they meet the following criteria:

- study participants met diagnostic criteria for schizophrenia as specified in the Chinese Classification of Mental Disorders,^[14] the WHO International Statistical Classification of Diseases (ICD),^[15] or the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM)^[16];
- the study used a standard two-tone auditory oddball task for eliciting P300, reported mean and standard deviation of P300 amplitude and latency at both the Cz and Pz locations, and compared P300 changes in subjects before and after treatment with antipsychotic medication; and
- the report did not duplicate data from prior reports.

As shown in Figure 1, 16 of the 28 full-text papers were excluded because the reports were using data that had appeared in an earlier report. In 4 cases the two evaluators initially disagreed about whether or not

Figure 1. Flowchart for identification of included studies



to include an article, but after re-reading the articles and comparing them with other articles (to determine whether or not they were overlapping) the reviewers were able to agree on the classification of the papers. This left 12 studies that were included in the meta-analysis.

2.2 Assessment of included studies

The included studies were independently assessed by two evaluators (the first two authors) who used the criteria for evaluating observational studies recommended in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.^[17] The following information was collected from each study: study design, study location, number of participants, participant demographic characteristics, whether or not subjects were in their first episode of illness, duration of illness, type of medication used, environment for assessing ERP, P300 measurement

methods, and statistical analysis methods. In situations where evaluators' opinions conflicted they reviewed the paper together to arrive at a consensus opinion.

2.3 Statistical analysis

The data were analyzed using Stata 11 Special Edition.^[18] The mean and standard deviation for P300 amplitude and latency were treated as continuous variables. The pooled standardized effect sizes (PSES) were calculated using standardized mean differences (SMD) and 95% confidence intervals (CI). If $P > 0.1$ and $I^2 < 50\%$ for a specific variable, the studies were judged to be homogeneous for this variable and a fixed-effects model was used; if these homogeneity criteria were not met for a particular variable, the studies were judged to be heterogeneous for the variable and a random-effects model^[19] was used. Publication bias was assessed using Egger's test, Begg's test and funnel plots.^[18]

Table 1. General information for 12 included studies

Reference	year of publication	time of study	subjects		mean age	first episode	mean duration of illness	mean PANSS score	antipsychotic medication		duration of treatment	instrument
			male	female					drug name	dose		
Chen ^[20]	1992	NA	19	16	35.1	NA	3.3 years	NA	NA	NA	2.0–4.6 months	NicoletBravo
Wang ^[5]	1998	NA	11	9	30	NA	1.9 years	NA	NA	NA	NA	NicoletCA-IV
Wang ^[21]	2003	NA	9	8	25	NA	10 months	NA	risperidone	NA	4 weeks	NicoletBravo
Liu ^{[22]a}	2004	NA	5	5	22.9	NA	17.9 months	90.2	clozapine	NA	4 weeks	Neuroscan
Liu ^{[22]b}	2004	NA	5	5	23.7	NA	20.8 months	86.3	clozapine	NA	4 weeks	Neuroscan
Zhu ^[6]	2005	NA	18	16	32.1	NA	0.4–1.5 years	NA	NA	225 mg/d ^c	6 months	Nicolet-Spirit
Chen ^[23]	2006	2003.2–2006.6	39	27	28	Yes	1.5 years ^d	111.5	NA	425 mg/d ^c	12 weeks	NicoletBravo
Sun ^[24]	2007	NA	34	0	33	NA	10 months	NA	risperidone	4–6 mg/d	6 months	NicoletBravo
Sun ^[24]	2007	NA	0	37	38	NA	10 months	NA	risperidone	4–6 mg/d	6 months	NicoletBravo
Wang ^[25]	2008	2005.1–2007.7	20	5	27.1	Yes	<20 months	66.8	risperidone	3.76mg/d	2 months	NicoletBravo
Wang ^[25]	2008	2005.1–2007.7	20	5	28.3	Yes	>20 months	66.8	risperidone	3.76mg/d	2 months	NicoletBravo
Yu ^[26]	2008	NA	27	22	29	Yes	1.6 years ^c	110	risperidone	1.5mg/d	12 weeks	NicoletBravo
Song ^[27]	2009	2008.8–2009.1	19	17	30.5	NA	5.2 years	≥60	risperidone	7.8 mg/d ^e	8 weeks	NicoletBravo
Song ^[27]	2009	2008.8–2009.1	18	18	30.1	NA	5.8 years	≥60	clozapine	4.9 mg/d ^e	8 weeks	NicoletBravo
Chen ^[28]	2010	2003–2005	49	9	27.9	Yes	19.2 months	NA	NA	NA	3 months	NicoletBravo
Gan ^[29]	2010	2006.4–2007.8	39	20	28.1	Yes	>2 years	NA	^f	NA	12 weeks	NicoletBravo
Gan ^[29]	2010	2006.4–2007.8	40	20	27.5	No	>2 years	NA	^g	NA	12 weeks	NicoletBravo

NA, not applicable

^apositive symptom group; ^bnegative symptom group; ^cchlorpromazine-equivalent dose; ^dmedian duration of illness; ^ehaloperidol-equivalent dose; ^ffirst generation antipsychotic medication and Tai-chi exercises; ^gfirst-generation antipsychotic medication without Tai-chi exercises

3. Results

The basic information about the 12 studies included in the meta-analysis is shown in Table 1. Five of the studies^[22,24,25,27,29] reported separately on different subgroups of patients so the data on each of the subgroups was included in the meta-analysis as a separate sample, making a total of 17 samples. A total of 611 patients with schizophrenia were enrolled in the 12 studies; all of these patients completed the initial evaluation of P300 amplitude and latency, and 502 of them (82.2%) completed the post-treatment evaluation of P300 amplitude and latency.

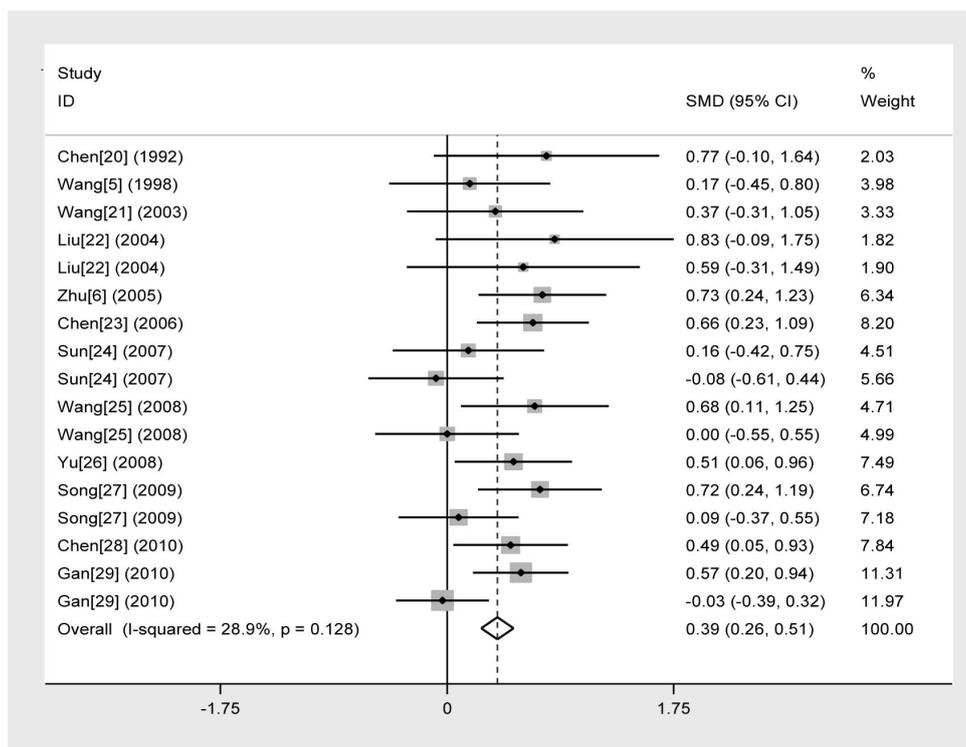
Comparison of the change in P300 amplitude during treatment in the 17 samples found that the results were not heterogeneous ($\chi^2=22.51$, $I^2=28.9\%$, $p=0.128$), so a fixed-effects model was used to compute the PSES for P300 amplitude. However the change in P300 latency with treatment in the 17 samples was heterogeneous across the studies ($\chi^2=47.73$, $I^2=66.5\%$, $p<0.001$), so a random-effects model was used to compute the PSES

for P300 latency.

As shown in Figures 2 and 3, after pooling the data from the included studies, treatment of patients with schizophrenia with antipsychotic medications was associated with a statistically significant increase in the P300 amplitude (PSES=0.388, 95% CI [0.264, 0.512], $z=6.14$, $p<0.001$) and a statistically significant decrease in P300 latency (PSES= -0.292, 95 % CI [-0.514, -0.070], $z=2.58$, $p=0.010$).

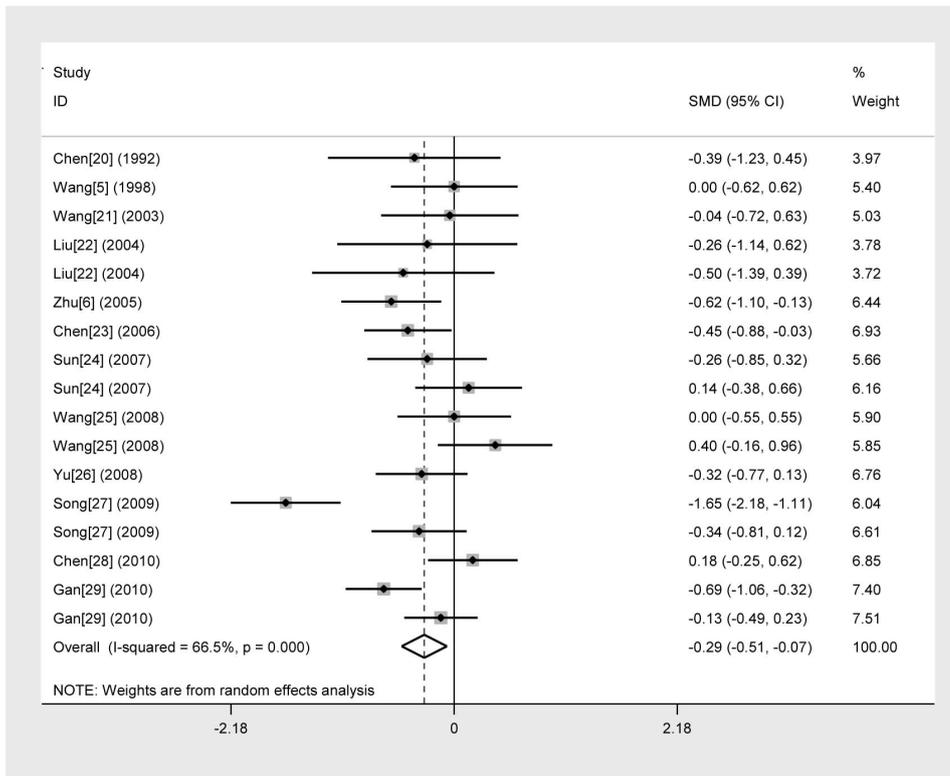
The funnel plots for the P300 amplitude and P300 latency results from the 17 samples reported in the 12 studies are shown in Figure 4. The symmetry of the plots indicates that there was little publication bias in these results. Begg's test and Egger's test results for changes in P300 latency (Begg's test, $p=0.837$; Egger's regression test, $p=0.466$) and for changes in P300 amplitude (Begg's test, $p=0.967$; Egger's regression test, $p=0.809$) also indicate that there was no publication bias.

Figure 2. Forest plot of post-treatment minus pre-treatment changes in P300 amplitude in patients with schizophrenia treated with antipsychotic medications



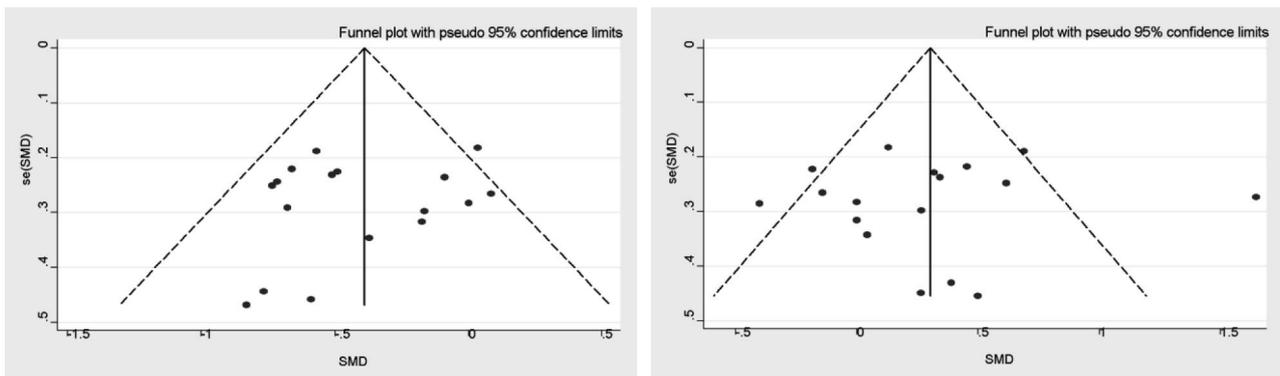
The horizontal lines represent 95% CI for the standardized mean difference (SMD) in each individual study. The size of the squares represents the weights given to the studies. The diamond shows the pooled standardized effect size (PSES) of all studies. The PSES was 0.388 (95% CI: 0.264, 0.512, $z=6.14$, $p<0.001$). It shows that the P300 amplitude was significantly increased after treatment with antipsychotic medication. Weights are computed using a fixed-effects model.

Figure 3. Forest plot of post-treatment minus pre-treatment changes in P300 latency in patients with schizophrenia treated with antipsychotic medications



The horizontal lines represent 95% CI for the standardized mean difference (SMD) in each individual study. The size of the squares represents the weights given to the studies. The diamond shows the pooled standardized effect size (PSES) of all studies. The PSES was -0.292 (95% CI: -0.514, -0.070, z=2.58, p=0.010). It shows that the P300 latency was significantly shortened after treatment with antipsychotic medication. Weights are computed using a random effects model.

Figure 4. Funnel plots for publication biases of the 17 samples reported in the 12 studies on P300 amplitude (left) and P300 latency (right)



The graphs show the distribution of the results from the 17 separate samples described in the 12 included studies according to the direction, magnitude and standard error of their effect sizes.

4. Discussion

4.1 Main findings

This meta-analysis of twelve electrophysiological studies in China among patients with schizophrenia who received treatment with antipsychotic medications found that antipsychotic treatment is associated with a small but significant increase in the amplitude of P300 (PSES=0.39) and a small but significant decrease in the latency of P300 (PSES= -0.29). Several electrophysiological studies^[2,3] report that patients with schizophrenia have lower P300 amplitude and longer P300 latency than controls and that these abnormalities are associated with cognitive deficits, so our finding of increased P300 amplitude and decreased P300 latency with treatment supports the results of treatment studies that find improvements in cognitive functioning with antipsychotic medications.^[6,7] But the magnitude of the change in the P300 indices is small (effect sizes of 0.2 to 0.5 are generally considered 'small'^[30]) so individual studies on this issue, many of which have relatively small sample sizes, have been contradictory or inconclusive.

We also found that the heterogeneity between studies in the results for P300 latency was greater than that for P300 amplitude. This suggests that treatment-related changes in P300 amplitude are more robust than treatment-related changes in P300 latency because they are more consistent across different settings and with different types of patients. This finding of greater heterogeneity in P300 latency across studies has also been reported in other studies.^[2,31]

Our main findings are different from those reported in two previous meta-analyses conducted in western countries. A meta-analysis by Bramon and colleagues^[31] that included 46 cross-sectional studies with a total pooled sample of 1443 patients compared medicated and non-medicated patients, and found significant differences in P300 amplitude but not in P300 latency. A meta-analysis by Jeon and colleagues^[32] that included 104 cross-sectional studies (the total number of subjects was not reported) found no significant differences in P300 latency or amplitude between subgroups of patients that were and were not medicated. The probable reason for the differences between our results and those of these earlier meta-analyses is that we included different types of studies. Unlike the western meta-analyses, our meta-analysis only included follow-up studies that compared P300 changes before and after treatment in the same patients, so our results were not confounded by demographic and clinical differences in the patients. Thus we believe that our result is a more valid assessment of the relationship between treatment with antipsychotic medication and changes in P300 indices.

4.2 Limitations

There was little evidence of publication bias and the use of change measures as the primary outcomes (i.e., the pre- versus post-treatment change in P300 latency and amplitude) minimized the potential confounding introduced by differences in the methods of assessing ERP at different research sites. However, there are several potential limitations that need to be considered when interpreting these results. The abstracts of articles in Chinese medical journals do not always provide clear information about the design and focus of the study, so it is possible that some suitable studies were excluded when reviewing the abstracts of articles identified by the electronic search. Only 82.2% of the participants in the 12 included studies completed the follow-up P300 assessments, but the study reports did not compare the P300 indices of patients who did and did not complete the studies so it is not possible to assess the potential biases introduced by the missing data. The 12 studies included patients with different demographic and clinical characteristics who used different medications at varying doses for different durations; the pooled sample was not large enough to adjust for these potential confounders. Also, the analysis did not consider adjunctive treatments (e.g., sleep medications, rehabilitation, cognitive behavioral therapy, etc.) that could potentially affect the P300 indices. Finally, the study is limited to Chinese patients so the results may not be relevant for patients with schizophrenia from other countries.

4.3 Significance

In contrast to meta-analysis from western countries — that are primarily based on cross-sectional studies — the current meta-analysis of follow-up treatment studies of schizophrenia in China finds a small but significant increase in P300 amplitude and a small but significant decrease in P300 latency with antipsychotic treatment. These findings suggest that P300 indices, particularly P300 amplitude, could be valuable biomarkers to monitor changes in cognitive functioning among patients with schizophrenia who receive treatment with antipsychotic medications. But prospective follow-up studies that simultaneously assess changes in these potential biomarkers and in objective measures of cognitive functioning during the course of treatment are needed to confirm the potential value of the P300 indices.

Conflict of interest

The authors report no conflict of interest related to this manuscript.

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• 论著 •

中国抗精神病药物治疗精神分裂症患者P300潜伏期和波幅变化的Meta分析

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摘要

背景 事件相关电位研究表明, 精神分裂症患者的认知功能损害与P300的潜伏期和波幅有关, 但尚不清楚这些认知功能的改变是否会随着药物治疗而改变。

目的 汇集中国的随访研究, 确定抗精神病药物治疗与P300成分改变的关系。

方法 手工和电子检索1982年1月至2011年12月在中国进行的、以中文或英文发表的文献, 内容为抗精神病药物治疗前后精神分裂症患者P300的潜伏期和波幅变化。2位评定者对12项符合Meta分析纳入标准的研究独立进行分析。12项研究中有17个样本的P300波幅峰值具有同质性, 因而采用固定效应模型计算汇集的标准化效应值 (pooled standardized effect size, PSES); 但P300潜伏期数值具有异质性, 因而采用随机效应模型计算PSES。采用Egger's和Begg's检验及倒漏斗图分析发表性偏倚。

结果 汇集样本的611例受试者中, 治疗前后完成P300潜伏期和波幅测试的502例 (82.2%) 纳入Meta分析。发现抗精神病药物治疗与P300波幅微小但显著的增加有关 (PSES=0.39, 95% CI [0.26, 0.51], $z=6.14$, $p<0.001$) 及P300潜伏期微小但显著的减少有关 (PSES= -0.29, 95% CI [-0.51, -0.07]; $z=2.58$; $p=0.010$)。无显著的发表偏移。

结论 既往西方的Meta分析主要是基于横断面研究, 与此不同, 中国的这一精神分裂症患者治疗随访研究的Meta分析发现P300波幅和潜伏期均随药物治疗而改变。提示P300成分, 特别是P300波幅, 可能是精神分裂症患者药物治疗期间监测认知功能变化的有价值的生物学标记。