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To cite this article: Mehmet Kemal Arıkan, Reyhan İlhan, Özden Orhan, Muhammed Taha Esmeray, Şenol Turan, Şakir Gica, Hasan Bakay, Oliver Pogarell, Kâşif Nevzat Tarhan & Barış Metin (01 May 2024): P300 parameters in major depressive disorder: A systematic review and meta-analysis, The World Journal of Biological Psychiatry, DOI: [10.1080/15622975.2024.2321554](https://doi.org/10.1080/15622975.2024.2321554)

To link to this article: <https://doi.org/10.1080/15622975.2024.2321554>



Published online: 01 May 2024.



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REVIEW ARTICLE



P300 parameters in major depressive disorder: A systematic review and meta-analysis

Mehmet Kemal Arıkan^a , Reyhan İlhan^a , Özden Orhan^a , Muhammed Taha Esmeray^a , Şenol Turan^b , Şakir Gıca^c , Hasan Bakay^c , Oliver Pogarell^d , Kâşif Nevzat Tarhan^e  and Barış Metin^e

^aProf. Dr. Mehmet Kemal Arıkan Psychiatry Clinic, Istanbul, Turkey; ^bDepartment of Psychiatry, Cerrahpaşa Medical School, Istanbul University, Istanbul, Turkey; ^cDepartment of Mental Health and Disease, MERAM School of Medicine, Necmettin Erbakan University, Konya, Turkey; ^dDepartment of Psychiatry, Division of Clinical Neurophysiology, Ludwig-Maximilians-University of Munich, Munich, Germany; ^eDepartment of Neurology, Medical Faculty, Uskudar University, Istanbul, Turkey

ABSTRACT

Objectives: Event-related potential measures have been extensively studied in mental disorders. Among them, P300 amplitude and latency reflect impaired cognitive abilities in major depressive disorder (MDD). The present systematic review and meta-analysis was conducted to investigate whether patients with MDD differ from healthy controls (HCs) with respect to P300 amplitude and latency.

Methods: PubMed and Web of Science databases were searched from inception to 15 January 2023 for case-control studies comparing P300 amplitude and latency in patients with MDD and HCs. The primary outcome was the standard mean difference. A total of 13 articles on P300 amplitude and latency were included in the meta-analysis.

Results: Random effect models indicated that MDD patients had decreased P300 amplitude, but similar latency compared to healthy controls. According to regression analysis, the effect size increased with the severity of depression and decreased with the proportion of women in the MDD samples. Funnel plot asymmetry was not significant for publication bias.

Conclusions: Decreased P300 amplitude may be a candidate diagnostic biomarker for MDD. However, prospective studies testing P300 amplitude as a monitoring biomarker for MDD are needed.

ARTICLE HISTORY

Received 3 November 2023
Revised 24 January 2024
Accepted 17 February 2024

KEYWORDS

Major depressive disorder; event-related potential; P300; oddball paradigm; meta-analysis

Introduction

Major depression (MDD) is a mental health disorder characterised by persistent low mood or loss of interest lasting at least two weeks, with symptoms including lack of energy, sleep disturbances, appetite changes, and difficulty concentrating thoughts (First et al. 2016). MDD affects 3.8% of the world's population and is the leading cause of disability worldwide (World Health Organization 2022). The leading cause of the economic and social burden associated with depression is treatment resistance (Wiles et al. 2014). The rate of treatment-resistant depression is approximately 30% (Kverno and Mangano 2021).

MDD presents heterogeneous symptoms, often shared with other disorders (Fried and Nesse 2015; Bilello 2016). In current clinical practice, the diagnosis of MDD is determined by diagnostic criteria based on

patient-reported symptoms (First et al. 2016). The lack of objective methods for diagnosing MDD can delay treatment initiation and adversely affect optimal treatment outcomes (Gaynes et al. 2009). Therefore, it is essential to identify biomarkers that can provide more objective assessment techniques to diagnose MDD (Biomarkers Definitions Working Group 2001). Although previous studies have shown that inflammatory, neurotransmitter, neurotrophic, neuroendocrine, metabolic, genetic, and epigenetic features, as well as EEG findings, may be potential candidates for MDD biomarkers, these findings are still quite inconsistent (Strawbridge et al. 2017; Hacimusalar and Eşel 2018; Kangas et al. 2022).

Event Related Potentials (ERPs) are simple and useful indicators that can detect neurophysiological abnormalities in the human brain (Polich 2007). Among

them, P300 is a positive potential with an amplitude of approximately 10 to 20 mV, usually with a peak around 300–500 ms (Polich 2007). The P300 is usually examined using an attention-focused difference task in which target stimuli are presented infrequently among repetitive standard stimuli, and subjects are asked to respond to the targets (Polich 2007). The amplitude of the P300 is related to cognitive functions such as attention, decision-making, stimulus salience, and working memory, whereas P300 latency is affected by information processing speed and may reflect the discrimination time required to interpret a stimulus as important or unimportant (Polich 2007).

Studies investigating P300 changes in MDD reports that P300 may be associated with cognitive ageing symptoms (Key et al. 2022), such as difficulties in attentional control and concentration (Kemp et al. 2010), memory (Ortiz et al. 2003; Li et al. 2014; Khan et al. 2022), and decision-making (Klawohn et al. 2022). It is worthy of note that while P300 is primarily associated with cognitive processing, it can also be modulated by affective state and trait factors. Emotional stimuli can influence P300 responses, reflecting the integration of emotional and cognitive processes (Hu et al. 2017; Moretta and Messerotti Benvenuti 2023). Besides, affective temperamental factors, depressive and cyclothimic temperaments have an opposing relationship with P300 latency indicating the variance in behavioural reactivity to the environmental stimuli (Poyraz et al. 2017). Overall, it can be concluded that the link between P300 changes and psychopathological symptoms in MDD is likely multifaceted, involving both cognitive and emotional aspects. Understanding these complex interactions can provide valuable insights into the underlying neurobiology of MDD and guide the development of targeted interventions for both cognitive and emotional symptoms.

Consistent with findings of cognitive dysfunction observed in MDD patients (Kalayam and Alexopoulos 1999), the P300 has been repeatedly reported to be altered in this patient population compared to healthy control groups (Gangadhar et al. 1993; Ancy et al. 1996; Vandoolaeghe et al. 1998; Bange and Bathien 1998; Kalayam and Alexopoulos 1999; Karaaslan et al. 2003; Köhler et al. 2011; van Dinteren et al. 2015; Shim et al. 2019; Jang et al. 2021). While some of these studies reported a decrease in the amplitude or increase in the latency of the P300 in depressed patients (Vandoolaeghe et al. 1998; Karaaslan et al. 2003; Mumtaz et al. 2015; Landes et al. 2018), one (Liu et al. 2014) found an increase in P300 amplitude as well as an increase in P300 latency in depression, and one (Xie et al. 2018)

found no significant difference in P300 between the depression group and healthy control groups.

Similar to depression, the decreased P300 amplitude is also detected in other psychiatric and neurocognitive disorders, such as bipolar disorder (Wada et al. 2019), schizophrenia (Earls et al. 2016), alcohol (Hamidovic and Wang 2019) and drug abuse (Euser et al. 2012), generalised anxiety disorder (Gordeev et al. 2013), Panic Disorder (Howe et al. 2014), obsessive compulsive disorder (Raggi et al. 2021), post-traumatic stress disorder (Javanbakht et al. 2011), attention deficit hyperactivity disorder (Mehta et al. 2020), borderline personality disorder (Penengo et al. 2022), antisocial personality disorder (Gao et al. 2009), Alzheimer's disease (Tarawneh et al. 2021), Parkinson's disease (Xu et al. 2022) and mild cognitive impairment (Tarawneh et al. 2021). Further, the prolonged P300 latency is also observed in bipolar disorder (Wada et al. 2019), schizophrenia (Earls et al. 2016), borderline personality disorder (Penengo et al. 2022), antisocial personality disorder (Gao et al. 2009), Alzheimer's disease (Tarawneh et al. 2021), Parkinson's disease (Xu et al. 2022), and mild cognitive impairment (Tarawneh et al. 2021).

Although these inconsistencies in the findings of previous studies have been addressed in some reviews, we currently do not know if p300 can be used as a biomarker in unipolar depression (Bruder et al. 2012; Olbrich and Arns 2013; Mumtaz et al. 2015; Kangas et al. 2022). To our knowledge, there is no meta-analysis focusing on the differences between MDD patients and healthy controls in terms of P300 findings. In the literature, we only found a meta-analysis comparing p300 in unipolar and bipolar depression patients (Zhong et al. 2019). In this meta-analysis, we aim to provide a quantitative synthesis of P300 study findings in MDD patients and explore the biomarker value of p300 in unipolar depression.

Materials and methods

In accordance with the PRISMA guidelines, the literature search was conducted using Pubmed and Web of Science (WoS) databases from inception to 15 January 2023. The following keywords were used in the logical operators: ('depression') AND ('electroencephalography' OR 'EEG') AND ('p300'). Based on the search terms, 194 articles were identified in Pubmed, while 153 articles were found in WoS. The first-step eligibility decisions were made by reviewing the titles and abstracts. In the second step, the eligibility decision was made after a full-text article reading by one of the authors. The results were double checked by our team. The PRISMA flow chart for the study selection can be found in Figure 1.

Eligibility criteria

The articles were reviewed according to the following inclusion criteria.

1. Case-control studies in which there will be at least one patient group and one healthy control group.
2. Samples aged above 18 years.
3. Patients had no diseases other than MDD, excluding subclinical anxiety.
4. The task to evoke P300 wave should be simple oddball paradigms, either auditory or visual paradigms.
5. P300 amplitude or latency should be reported in mean and standard deviation.

Articles were excluded according to criteria described in below. Most of the excluded articles were found ineligible due to out of scope, pointed out in Table 1 in more detail.

1. Lack of a healthy control group.
2. Diagnosis of bipolar depression, psychotic depression, and other psychiatric and neurological disorders.
3. Paediatric and adolescent samples.
4. Studies using task other than the classical oddball paradigm, such as the Flanker task, Stroop task, reward learning task, monetary incentive delay task, gambling task, three-tone auditory task, complex oddball task, novelty oddball task, passive oddball task.
5. Studies reporting only statistical significance results between two groups without giving group means and standard deviations.

Data extraction

The extracted information from articles was the sample size of each group, age, gender, task type to evoke P300, mean and standard deviation of P300 amplitude

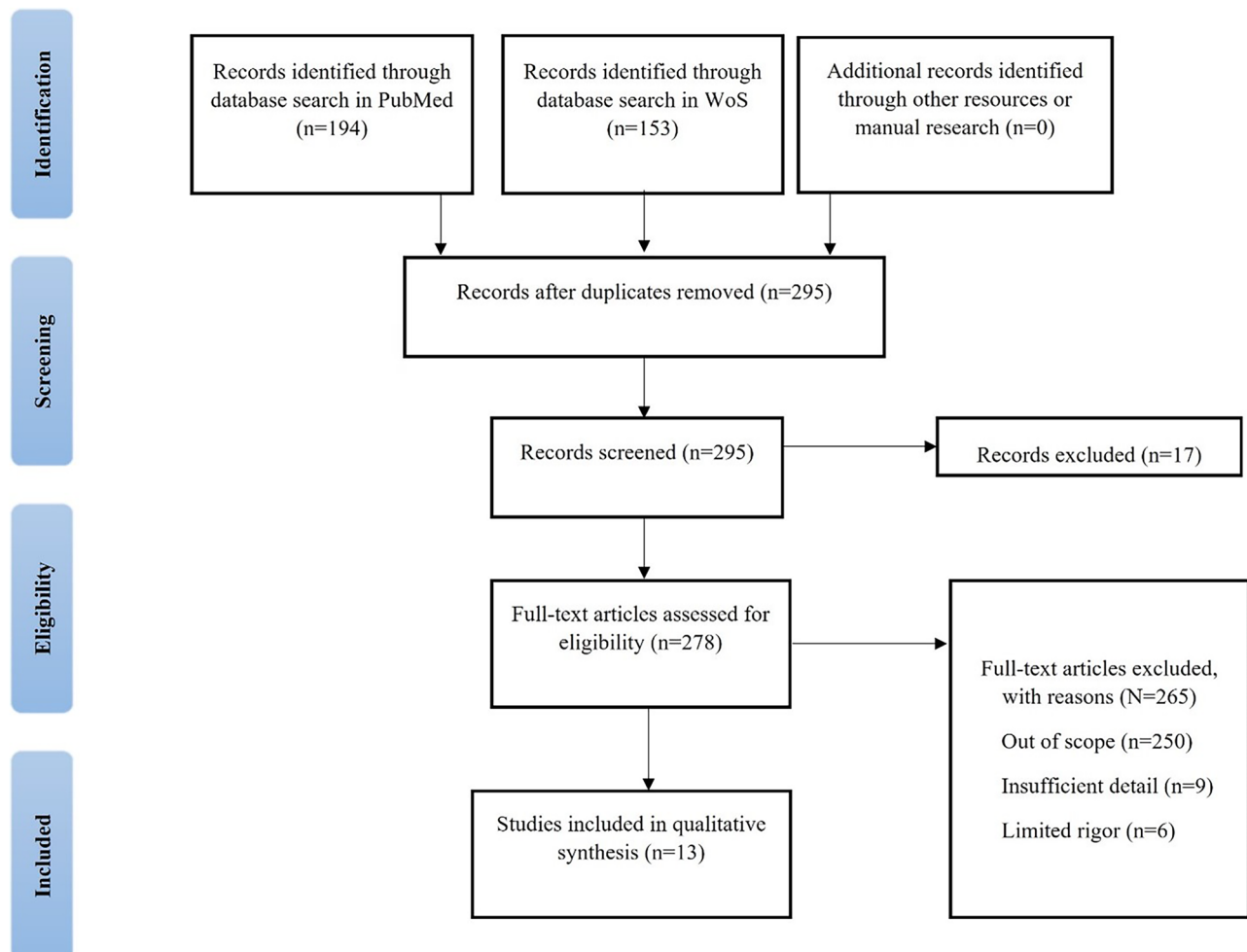


Figure 1. PRISMA flowchart.

and latency, electrode placement, diagnostic criteria, and severity of depression evaluated by rating scales. To reduce bias and improve accuracy, the data extraction and study selection processes were double-checked by two authors.

Table 1. Excluded studies due to 'Out of Scope'.

Reasons for out of scope	Number of studies excluded
Absence of depression in study participants	141
Lack of control (healthy) condition	42
Non-adult population	13
Not a case control study article	12
Absence of P300 measurement	11
Language other than English	10
Lack of standardised diagnostics for MDD	8
Not classical oddball paradigm	7
Presence of comorbid psychiatric disorder	3
Total	250

Table 2a. Study characteristics.

Study Name	Year	Oddball Paradigm	Amplitude/Latency	Electrode	MDD (n)	HC (n)	Age	HDRS	Female %
(Bange and Bathien 1998)	1998	Visual	Both	CZ,PZ	12	20	50.7	28.8	50
(Ancy et al. 1996)	1996	Auditory	Both	CZ	17	15	41.4	28.6	52.9
(Gangadhar et al. 1993)	1993	Auditory	Both	CZ	17	22	38.5	-	64.7
(van Dinteren et al. 2015)	2015	Auditory	Amplitude	PZ	1008	336	37.8	21.8	56.8
(Karaaslan et al. 2003)	2003	Auditory	Both	CZ	20	20	34.8	32.8	40
(Kalayam and Alexopoulos 1999)	1999	Auditory	Both	PZ	49	22	74.8	22.5	72.3
(Köhler et al. 2011)	2011	Auditory	Both	Average	19	25	70.9	-	70
(Shim et al. 2019)	2019	Auditory	Both	CZ,PZ	67	39	42.1	-	64.2
(Kutcher et al. 1987)	1987	Auditory	Both	CZ	22	74	41	-	54.5
(Patterson et al. 1988)	1988	Auditory	Latency	PZ	8	15	65.9	-	-
(Sumi et al. 2000)	2000	Auditory	Latency	PZ	35	39	68.2	21.7	57.1
(Jang et al. 2021)	2021	Auditory	Amplitude	PZ	33	30	40	20.2	66.6
(Vandoolaeghe et al. 1998)	1998	Auditory	Both	CZ	35	11	53.4	24.1	60

Table 2b. Group descriptive statistics for latency and amplitude measures.

Study	Measure	Electrode	MDD (M)	MDD (SD)	MDD (n)	HC (M)	HC (SD)	HC (n)
Bange and Bathien 1998	amp	Cz	6.9	4.97	12	10.1	6.23	20
Bange and Bathien 1998	amp	Pz	10.6	6.01	12	14.1	7.26	20
Bange and Bathien 1998	lat	Cz	444	72.3	12	393	41.1	20
Bange and Bathien 1998	lat	Pz	444	67.9	12	400	45.6	20
Ancy et al. 1996	amp	Cz	6.2	3.8	17	10.5	6.3	15
Ancy et al. 1996	lat	Cz	334.1	31.2	17	333.2	28.7	15
Gangadhar et al. 1993	amp	Cz	6.5	4.4	17	11.5	5.8	22
Gangadhar et al. 1993	lat	Cz	336.3	26.4	17	338.9	22.2	22
van Dinteren et al. 2015	amp	Pz	9.51	5.93	1008	11.73	7.31	336
Karaaslan et al. 2003	amp	Cz	7.72	2.96	20	12.97	4.43	20
Karaaslan et al. 2003	lat	Cz	352.58	32.36	20	307.2	45.08	20
Kalayam and Alexopoulos 1999	amp	Pz	4	2.4	49	4.6	1.7	22
Kalayam and Alexopoulos 1999	lat	Pz	383.1	44.9	49	341.6	28.1	22
Köhler et al. 2011	amp	mean	6.9	3.8	19	8.2	4.3	25
Köhler et al. 2011	lat	mean	426	84	19	387	31	25
Shim et al. 2019	amp	Cz	10.31	4.12	67	11.21	3.92	39
Shim et al. 2019	amp	Pz	9.42	3.54	67	10.24	3.72	39
Shim et al. 2019	lat	Cz	349.51	35.74	67	355.79	24.59	39
Shim et al. 2019	lat	Pz	366.22	35.52	67	366	27.71	39
Kutcher et al. 1987	amp	Cz	6.94	3.06	22	8.92	2.85	74
Kutcher et al. 1987	lat	Cz	305	18.8	22	298	21.1	74
Patterson et al. 1988	lat	Cz	356.8	24.3	8	372.9	36.3	15
Patterson et al. 1988	lat	Pz	364	28.5	8	377.9	34.4	15
Sumi et al. 2000	lat	Pz	356.3	27	35	377.2	25.5	39
Jang et al. 2021	amp	Pz	8.87	3.72	33	9.95	3.52	30
Vandoolaeghe et al. 1998	amp	Cz	7.4	5.6	35	11.1	8.6	11
Vandoolaeghe et al. 1998	lat	Cz	339	38	35	306	30	11

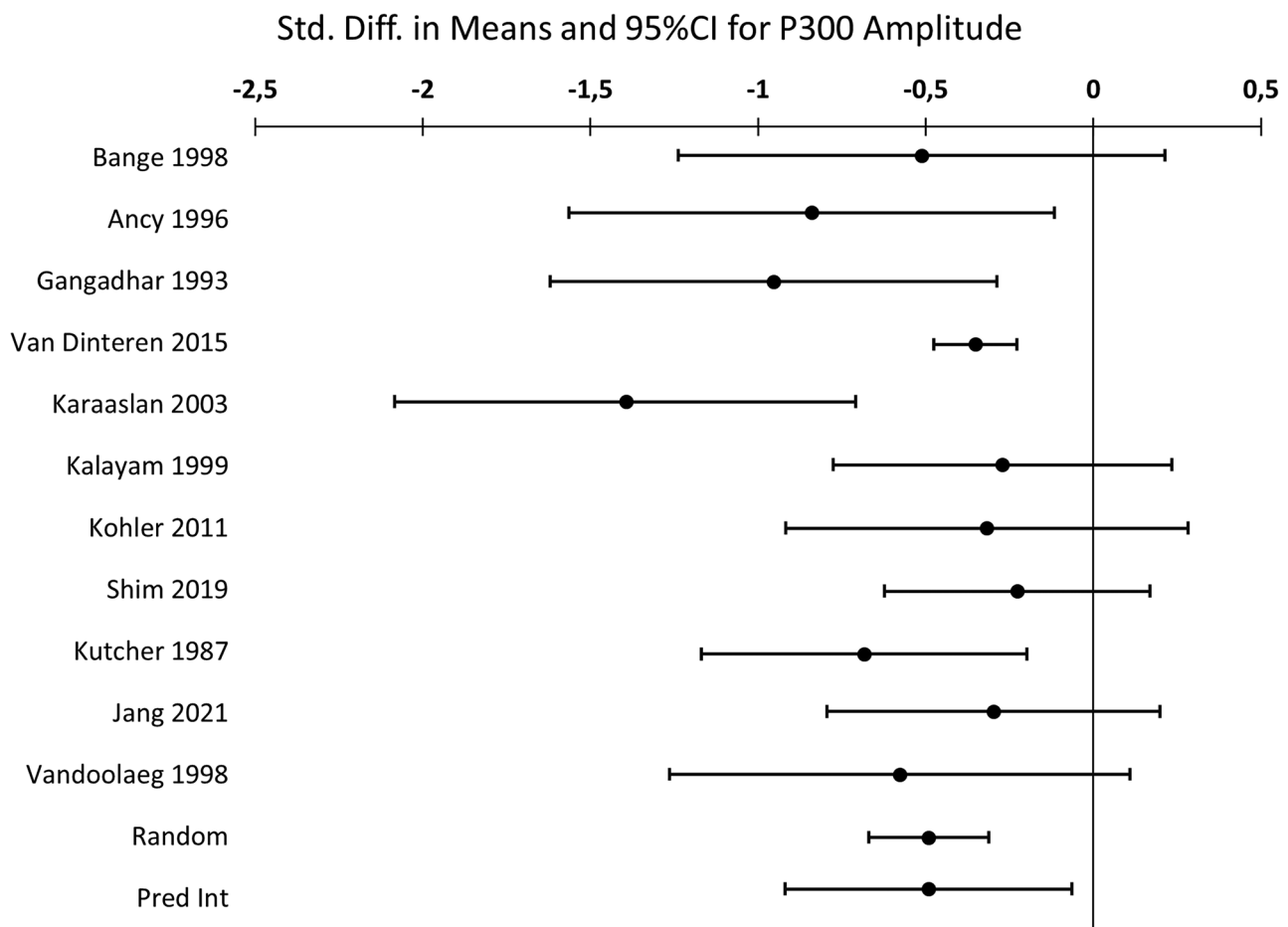
Statistical analysis

All the statistical analysis was performed on Comprehensive Meta-Analysis Software - CMS (Version 4, (Borenstein et al. 2022).

The random effect model was chosen due to presumed heterogeneity. The standardised mean difference was used as the outcome variable in the analysis and is used in the present study as an effect size. Two forest plots were calculated for amplitude and latency separately. Secondly, the association between effect size and age, gender, and depressive scores evaluated by Hamilton Depression Rating Scale (HDRS) were investigated by regression analysis. HDRS was chosen as it was the most commonly reported scale. The studies reporting HDRS results can be found in Table 2a. Finally, the studies

Table 3. Random effects model for comparison of P300 amplitude between MDD patients and healthy controls.

Model	Study Name	Comparison	Electrode	Std diff in means	Standard error	Variance	Lower limit	Upper Limit	Z-Value	p-Value
	Bange 1998	Amplitude	PZ	-0.513	0.371	0.137	-1.239	0.214	-1.383	0.167
	Ancy 1996	Amplitude	CZ	-0.84	0.369	0.137	-1.564	-0.116	-2.273	0.023
	Gangadhar 1993	Amplitude	CZ	-0.954	0.341	0.116	-1.621	-0.287	-2.802	0.005
	van Dinteren et al. 2015	Amplitude	PZ	-0.352	0.063	0.004	-0.476	-0.228	-5.559	0.000
	Karaaslan et al. 2003	Amplitude	CZ	-1.394	0.353	0.124	-2.084	-0.709	-3.953	0.000
	Kalayam 1999	Amplitude	PZ	-0.271	0.258	0.066	-0.776	0.234	-1.053	0.292
	Köhler et al. 2011	Amplitude	FZ,CZ,PZ	-0.318	0.306	0.094	-0.918	0.283	-1.037	0.300
	Shim 2019	Amplitude	PZ	-0.227	0.202	0.041	-0.623	0.169	-1.125	0.260
	Kutcher et al. 1987	Amplitude	CZ	-0.683	0.248	0.061	-1.169	-0.198	-2.757	0.006
	Jang et al. 2021	Amplitude	PZ	-0.298	0.254	0.064	-0.795	0.199	-1.174	0.240
	Vandoolaeg 1998	Amplitude	CZ	-0.578	0.351	0.123	-1.265	0.11	-1.646	0.100
Random				-0.491	0.091	0.008	-0.67	-0.312	-5.38	0.000
Pred Int				-0.491			-0.919	-0.064		

**Figure 2.** The forest plot of effect sizes for P300 amplitude.

reporting significant or null results were compared in a funnel plot graphic to check the publication bias.

Results

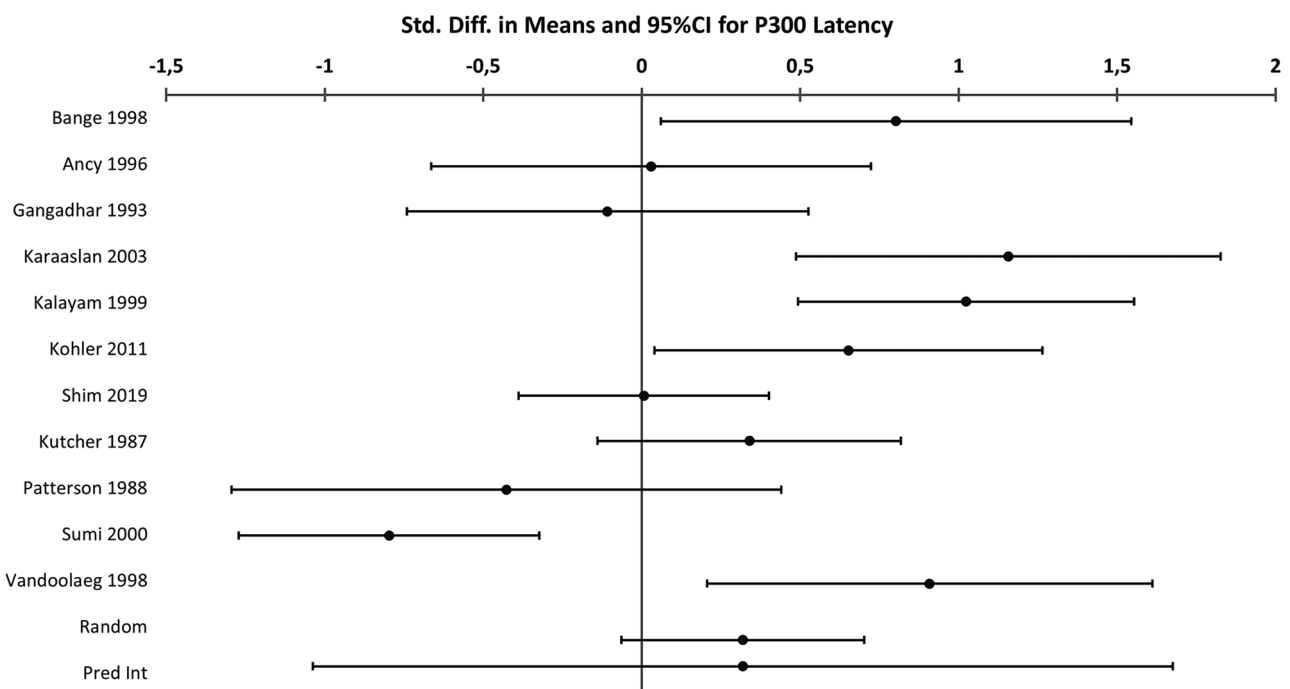
Study characteristics

The study characteristics and descriptive statistics can be found in [Tables 2a](#) and [2b](#). Based on the

eligibility criteria, 13 case-control studies were included in the analysis. These studies compared the patients with MDD ($n=1306$) and HCs ($n=681$). The mean (SD) age ($k=13$) of subjects was 51.43 (15.66), and the mean (SD) rate of female patients ($k=11$) was %59.01 (9.60) and the mean (SD) depressive symptoms evaluated by HDRS ($k=7$) was 25.54 (4.59). From 13 studies, 17 amplitude, and 18 latency measurements were recorded from, Cz, or Pz electrodes.

Table 4. Random effects model for comparison of P300 latency between MDD patients and healthy controls.

Model	Study Name	Comparison	Electrode	Std diff in means	Standard error	Variance	Lower limit	Upper Limit	Z-Value	p-Value
	Bange 1998	Latency	PZ	0.802	0.379	0.143	0.060	1.545	2.119	0.034
	Ancy 1996	Latency	CZ	0.030	0.354	0.126	-0.664	0.724	0.085	0.933
	Gangadhar 1993	Latency	CZ	-0.108	0.323	0.104	-0.741	0.526	-0.334	0.739
	Karaaslan et al. 2003	Latency	CZ	1.157	0.342	0.117	0.487	1.826	3.385	0.001
	Kalayam 1999	Latency	PZ	1.024	0.271	0.073	0.493	1.554	3.783	0.000
	Köhler et al. 2011	Latency	M	0.652	0.312	0.097	0.041	1.264	2.090	0.037
	Shim 2019	Latency	PZ	0.007	0.201	0.041	-0.388	0.401	0.033	0.974
	Kutcher et al. 1987	Latency	CZ	0.340	0.244	0.060	-0.139	0.818	1.392	0.164
	Patterson 1988	Latency	PZ	-0.427	0.442	0.196	-1.294	0.440	-0.965	0.334
	Sumi et al. 2000	Latency	PZ	-0.797	0.242	0.059	-1.271	-0.323	-3.296	0.001
	Vandoolaeg 1998	Latency	CZ	-0.908	0.358	0.128	0.206	1.611	2.534	0.011
Random				-0.319	0.196	0.038	-0.064	0.702	1.631	0.103
Pred Int				-0.319			-1.037	1.676		

**Figure 3.** The forest plot of effect sizes for P300 latency.

We included Pz P300 measures when available; if not, we included Cz ones. One study reported the mean of all electrodes and therefore it was used (Köhler et al. 2011).

P300 amplitude and latency

The random-effects model showed that patients with MDD had reduced amplitude than the P300 amplitude of HCs with an effect size of 0.49 (CI: -0.67, -0.31) (Table 3 and Figure 2). As for P300 latency, patients with MDD did not differ from HCs significantly (effect size = 0.32, CI: -0.06 to 0.70) (Table 4 and Figure 3).

Regression analysis

The relationship between effect size for amplitude and possible predictors, namely, age, gender, and severity of depression were further analysed. The meta-regression did not show a significant effect of age on the effect sizes ($p > 0.5$). However, there was a negative relationship between the severity of depression and the effect sizes (7 studies reporting HDRS included $p = 0.003$) in that the difference between MDD and HCs increases, as the severity of depression increases (Table 4 and Figure 4). As for gender, there was a positive relationship between the rate of females and the effect sizes ($p = 0.025$) in that the difference between MDD and

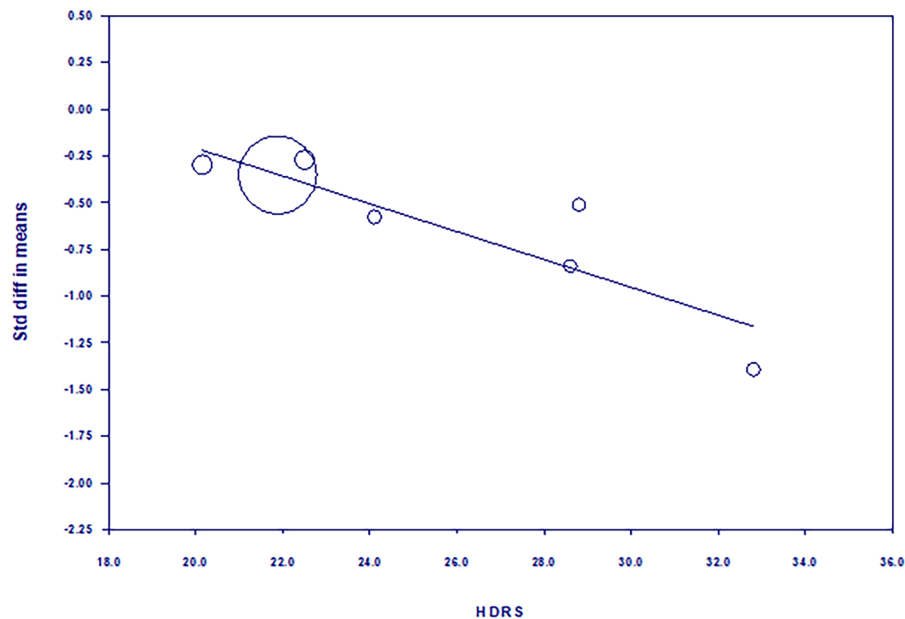


Figure 4. The meta regression analysis for the effect of HDRS scores on effect sizes.

Table 5. Statistics for the effects of depressive symptoms and female percentage on effect sizes.

	Models	Covariate	Coefficient	Std.Error	95% Lower	95% Upper	Z	p (2-sided)
Meta-regression results	HDRS	Intercept	1.28816	0.5617	0.1806	2.3825	2.28	0.0225
		HDRS	-0.0745	0.0249	-0.1232	-0.0258	-3.00	0.0027
	Female %	Intercept	-1.8913	0.6409	-3.1475	-0.6352	-2.95	0.0032
		Female	0.0239	0.0107	0.0030	0.0449	2.24	0.0250

HCs decreased as the sample had more females (Table 5 and Figure 5).

Publication bias and leave-one-out analysis

The funnel plot of all included studies to the amplitude analysis was visually inspected to detect potential publication bias. A more asymmetrical distribution regarding the mean effect size indicates publication bias. It has been observed that there is an asymmetrical distribution in the funnel plot (Figure 6). However, fail-safe N was detected, as meaning that 149 more studies are necessary to nullify the significant results. Using Duval and Tweedie's trim and fill method we aimed to impute the effect of missing studies on effect sizes. The imputed point estimate was -0.37822 (CI: $-0.58, -0.17$) (Borenstein et al. 2022). In addition we repeated the analysis multiple times after leaving one of the studies out until all the studies were removed and checked if removal of one of these studies made a large impact to the summary result. With this method we did not detect any significant change in the calculated mean effect size for the amplitude difference. For each study removed, calculated mean effect size remained significant.

Electrode position effect

In a subsequent analysis we separately calculated mean effect size for studies reporting results for Pz and Cz electrode. For Pz electrode the mean effect size was -0.340 (CI: $-0.45, -0.23$; 5 studies). While for Cz electrode the effect size was -0.69 (CI: $-0.99, -0.40$; 7 studies).

Discussion

Historically, the present study is the first meta-analysis of MDD case-control studies measuring P300 wave during the classical oddball paradigm. The most similar is a meta-analysis of comparative studies on BD and MDD patients with or without HCs (Zhong et al. 2019). It included seven studies with the HC group and concluded that depressed MDD patients had delayed latency and smaller amplitude than HCs (Zhong et al. 2019). Our analysis included more studies, thus more MDD patients and HCs. Similar to previous meta-analysis, we also found that relative to HCs, patients with MDD had decreased P300 amplitude. However, our results differ in that MDD patients did not show longer latency than HCs.

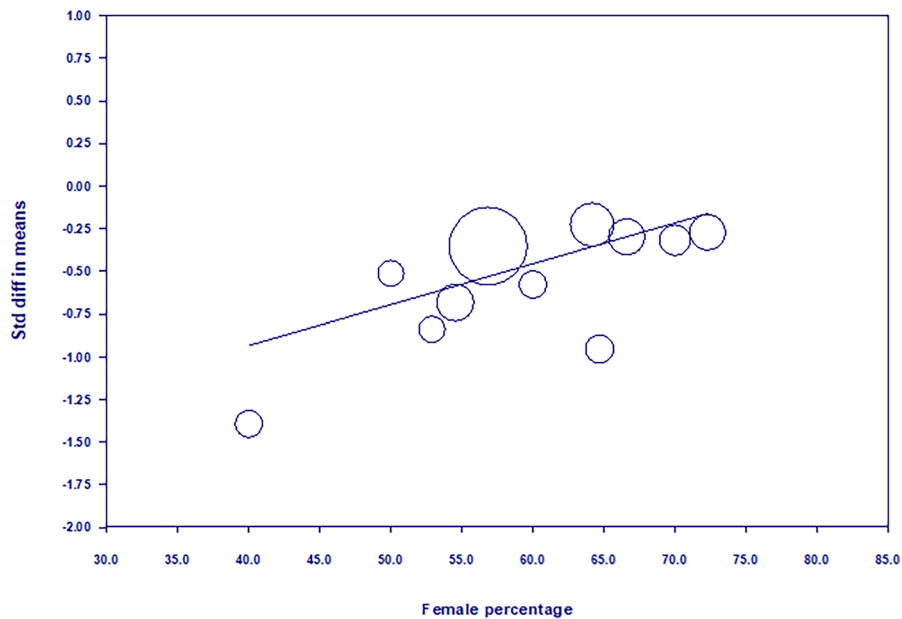


Figure 5. The meta regression analysis for the effect of female percentage on effect sizes.

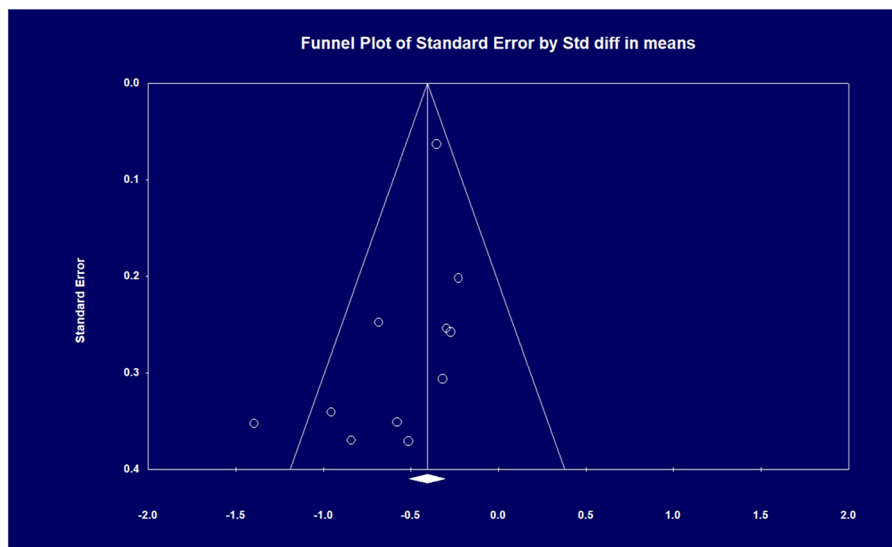


Figure 6. The funnel plot for analysis of publication bias.

As the literature reveals, the smaller amplitude of the P300 wave is seen in other mental disorders. This finding has been demonstrated by repeated studies, especially in schizophrenia and depression (Blackwood et al. 1987; Ford et al. 1994). In studies comparing depressed patients with and without psychotic features, it was reported that P300 amplitude was smaller in the psychotic depression group and negatively correlated with psychotic symptoms (Santosh et al. 1994; Karaaslan et al. 2003). In another study, a negative correlation was found between P300 amplitude and HDRS score in schizophrenia patients (Blackwood et al. 1987). However, these findings are not sufficient to explain

the decreased P300 amplitude only with psychotic symptoms in depressive patients. Because different pathophysiological mechanisms have been shown to affect P300 amplitude in schizophrenia and depression patients (Wagner et al. 2007). According to these findings, it could be argued that the smaller P300 amplitude is not a specific diagnostic biomarker for MDD. Nevertheless, machine learning studies revealed that combining several P300 features obtained from different paradigms yields diagnostic sensitivity of MDD up to 87%, along with high accuracy (Jang et al. 2023).

In the literature, the normalisation of P300 amplitude is possible with treatment. One study compared

responders and non-responders to 12-week sertraline treatment regarding P300 measures. They found that P300 amplitude increased after treatment only in the responding group and became equal with HCs (İşintaş et al. 2012). In another study, MDD patients with or without psychotic features were compared with HCs before and after treatment. Baseline reduced P300 amplitude normalised after treatment but only for psychotic MDD patients (Karaaslan et al. 2003). In a previous P300 study with schizophrenia and depression patients, a similar increase in P300 amplitude was observed with treatment in the psychotic depression group (Blackwood et al. 1987). However, the decreased P300 amplitude observed in schizophrenia did not normalise with treatment (Blackwood et al. 1987; Ford et al. 1994). Considering that abnormalities in P300 amplitude are also seen in mental disorders other than depression and that these abnormalities improve with treatment, it can be concluded that P300 measurements may be considered state markers and be preferred in monitoring the course of treatment rather than making a diagnosis.

Another conclusion that can be drawn from our findings is the positive relationship between the depression scores of the patients measured by HDRS and the effect size. Accordingly, as the severity of depression increased, the P300 difference between patients and controls became larger. This finding is consistent with some studies conducted with MDD patients (Tripathi et al. 2015). Considering the relationship between the p300 and attention and stimulus processing, it could be suggested that P300 abnormalities can aid clinicians in decisions on the severity of depression.

Regarding gender factor, our analysis found a negative relationship between effect size and the percent of female patients meaning that the abnormality in the P300 measure is more apparent in male depressed patients. The sex difference in the P300 measure is seen in healthy subjects depending on age in that men experience more rapid change than women in P300 latency (Hirayasu et al. 2000). Among sex hormones, oestrogen, progesterone, and testosterone are known to affect cognition (Gurvich et al. 2018). Studies showed that P300 measures show intra-individual variance in females and males depending on hormone levels. For instance, pre-menopausal young females had heightened P300 amplitude and shortened P300 latency during the periovulatory phase, characterised by increased oestrogen and decreased progesterone (Pompili et al. 2016). As for the post-menopausal period, a study on women with cognitive decline

differed HCs for P300, yet after hormone replacement therapy, i.e. oestrogen and progesterone, the delayed P300 latency shortened (Anderer et al. 2005). As for the males, the deficiency in sex steroid hormones, i.e. hypogonadism, is associated with abnormalities in P300 amplitude and latency (Ozata et al. 1999; Ulas et al. 2006).

Strengths and limitations

In this analysis, there are limitations worthy of mentioning. First, we included studies conducted with older adults. However, the possible effect of age factor on effect size is checked. No relationship between age and effect size is found. Provided that the control group matched with the depression group, our results revealed that the P300 abnormalities of MDD patients are observable in all ages. Secondly, we could not extract HDRS scores from all studies. In addition, these scores reflect the overall MDD sample rather than gender-based groups. Thus, we could not rule out whether depressed female patients had less severe symptoms, so the effect size decreased for this population. Third, we could not remove the studies conducted with patients on medication, which constitutes the half of the articles. However, this issue was also a confounder for the previous meta-analysis comparing unipolar and bipolar depression patients (Zhong et al. 2019). Forth, the meta-analysis results can be affected by several sources of bias that involve the publication of predominantly positive findings and study selection and data extraction steps. In this study, we tested the effects of publication bias using funnel plot analysis and observed minimal impact. In addition, we aimed to minimise the bias during the study selection and data extraction steps by cross-checking the accuracy of these steps by two authors. Finally, there was considerable amount of between study heterogeneity. For instance, we found that the mean effect size was greater for studies reporting P300 at CZ electrode. Other factors that could potentially introduce bias include differences in preprocessing steps and calculation methods of P300 peaks.

This meta-analysis attempted to show the P300 measurements between MDD patients and healthy controls. Among 13 studies, we found that patients with MDD had smaller P300 amplitude than HCs. However, the standardisation of p300 measurement is required to reduce between-study heterogeneity. For instance, we found that the mean effect size was greater when only studies reporting the results for Cz

electrode were used. Finally, more studies are needed to detect whether p300 is a state or trait biomarker in depression. In other words, the effects of medications and depression remission to p300 amplitude should be further studied.


Acknowledgements

None declared.

Statement of interest

None to declare.

ORCID

Mehmet Kemal Arıkan  <http://orcid.org/0000-0003-1500-6555>
 Reyhan İlhan  <http://orcid.org/0000-0002-2117-8276>
 Özden Orhan  <http://orcid.org/0000-0003-0529-2789>
 Muhammed Taha Esmeray  <http://orcid.org/0000-0002-8271-9662>
 Şenol Turan  <http://orcid.org/0000-0002-8684-2617>
 Şakir Gica  <http://orcid.org/0000-0001-7387-8840>
 Hasan Bakay  <http://orcid.org/0000-0002-8864-2942>
 Oliver Pogarell  <http://orcid.org/0000-0001-6455-4190>
 Kâşif Nevzat Tarhan  <http://orcid.org/0000-0002-6810-7096>

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