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REVIEW

The Electrophysiology of Semantic Processing in Individuals with Autism Spectrum Disorder: A Meta-Analysis

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ABSTRACT

Language difficulties vary widely among people with autism spectrum disorder (ASD). However, the semantic processing of autistic person and its underlying electrophysiological mechanism are still unclear. This meta-analysis aimed to explore the disturbance of semantic processing in patients with ASD. PubMed, Web of Science, and Embase were searched for event-related potential (ERP) studies on semantic processing in autistic people published in English before September 01, 2022. Pooled estimates were calculated by fixed-effects or random-effects models according to the heterogeneity using Comprehensive Meta-Analysis 2.0. The potential moderators were explored by meta-regression and subgroup analysis. This meta-analysis has been registered at the Prospero International Prospective Register of Systematic Reviews (no. CRD 42021265852). A total of 14 articles and 18 studies, including 254 autistic people and 262 neurodevelopmental people were included in this meta-analysis. Compared to the comparison group, autistic people showed an overall reduced N400 amplitude (Hedges' g = 0.350, $p < 0.001$) in response to linguistic stimuli instead of non-linguistic stimuli. The N400 amplitude was affected by verbal intelligence and gender. The reduced overall N400 amplitude in autistic people under linguistic stimuli suggests a linguistic-specific deficit in semantic processing in individuals of autism. The decrease of N400 amplitude might be a promising indication of the pool language capacity of autism.

KEYWORDS

Autism spectrum disorder; N400; P600; semantic; event-related potential; meta-analysis

Introduction

Autism spectrum disorder (ASD) is a range of neurodevelopmental conditions characterized by impairments in social interaction as well as restricted/repetitive behavior and interests [1]. Although challenges with language is no longer a core symptom of ASD, it is still more extensive than assumed in autistic individuals. In addition, there is marked variability in language proficiency of ASD patients, ranging from silent to verbally fluent. Compared to language production, language comprehension difficulties may be more severe and may serve as an early sign of ASD [2,3]. Semantic processing, which means understanding and categorizing the meaning of stimulus, is considered to play a vital role in language comprehension [4]. Some studies suggested that semantics might provide a foundational language skill for social interactions and social skills in children with autism [5]. Event-related potential (ERP) with millisecond resolution is an efficient and sensitive technique for characterizing subtle differences in semantic processing [6]. As reflecting the neural mechanism of language comprehension, the N400 and the P600 are the most important ERP components in language progressing [4,7].

The N400 component is one of the most powerful tools used for semantic processing and integration research. It was first noted by Kutas and Hillyard as a language measure [8]. Although it is a negative peaking over the central-posterior electrode sites, it need not be negative in absolute terms [9]. The N400 effect refers to a difference ERP created via subtraction of a congruent condition from an incongruent one [10] and reflects the activation of related semantic networks [11]. The N400 response is often elicited by two paradigms. The semantic-anomaly paradigm generates a narrative with contextually congruent or incongruent sentence-final words. The amplitude of the N400 is greater for the incongruent condition because integration is difficult in incongruent context [12]. The semantic-priming paradigm provides a related or unrelated word before a target word and the priming word is considered to be the context for the target word to be integrated [13]. The decrease in the amplitude of N400 reflects the response to the target word, which is semantically related to the previous words [14]. Both of the two paradigms reflect the process of semantic integration of the critical word with the working context. Another theory supported that the N400 response reflects facilitated activation of the long-term memory as N400 is sensitive to word frequency [15]. Generally speaking, high-frequency and early-acquired words result in shorter N400 latency and a smaller N400 amplitude relative to less frequent words as they are easier to access from memory [16]. In addition, other factors that may alter the N400 amplitude include language proficiency and modalities [9]. Now, the function of N400 has been expanded to reflect meaning processing more broadly. Nonlinguistic context such as picture sequences was found to elicit N400 effect. However, the N400 effects elicited by nonlinguistic context is more frontally-distributed in scalp topography [17].

So far, there are considerable variabilities in N400 response among individuals with autism. A few studies have concluded that autistic people exhibit decreased or disappeared N400 effect, suggesting destruction of the neural response in language processing [5,18]. Meanwhile, in some studies, the N400 effect is typical in autistic people, with more significant negativity elicited by the incongruent stimulation [19–21]. By comparing the N400 component between autistic and non-autistic group, some studies found that autistic people showed abnormal N400 response [22]. Previous studies have confirmed that N400 could also be elicited by paradigms represented with the nonverbal stimuli such as visual narratives and environmentally sound. Some studies suggested that autistic people experience deficits in the semantic processing of language, but the semantic processing of non-verbal stimuli is intact [23,24]. While some literature suggested that autistic person showed a potential benefit of using verbal material but a medium difficulty with visual long-term memory [25].

P600, a positive deflection in centro-parietal is assumed to be a family member of the late positive components (LPC). P600 is considered as another important language-related ERPs and was first characterized in the context of syntactic processing [26]. Recent studies suggested that P600 might reflect more general conflict monitoring mechanisms rather than purely syntactic processes [27]. Previous studies have not yet determined whether autistic individuals present abnormal P600 under semantic or syntactic violation conditions.

The inconsistent results of language related ERPs in ASD may be derived from the heterogeneity generated by individual differences, modalities, and stimulus materials. The individual heterogeneity is assumed to originate from age (children/adolescents or adults), diagnosis (autism or Asperger syndrome), and cognitive ability. For the heterogeneity in modalities, the N400 effect was elicited either from unimodal tasks (visual or auditory) or from cross-modal paradigms given the high multisensory nature of language cues. For the heterogeneity in materials, the N400 effect was obtained from lexical associative priming or sentence-level congruity.

To date, evidence assessing the language-related ERPs in ASD is lacking, especially when compared the language-related ERPs among different experimental stimulus and paradigms. This meta-analysis therefore updates the current knowledge on semantic processing disturbance in patients with autism. The aims of this study were (1) to examine the neural characteristics of semantic processing in autistic people; (2) to explore the factors affecting semantic processing ERP feature in patients with ASD.

Methods

This review was registered at the Prospero International Prospective Register of Systematic Reviews (PROSPERO no. CRD 42021265852) and followed guidance of conducting and reporting systematic reviews from the Cochrane handbook and the PRISMA checklist assessed by the editorial team of PRISMA.

Search protocol

The articles were searched before September 01 2022 in PubMed, Web of science, and Embase. The search terms we used were MeSH phrases and text words related to autism spectrum disorder ("Autistic disorder" or "Asperger Syndrome" or "Autistic Spectrum Disorder" or "Disorder, Autistic Spectrum"), semantics ("semantic" or "language" or "linguistics") and Event Related Potential ("N400" or "P600" or "Potential, Event-Related" or "Potential, Event Related"). The combination of search terms was listed in Suppl. Table S1.

Selection criteria

Publications were only included in the analysis if: (1) studies published in English with full text available; (2) the study included between-group comparison with autistic and non-autsitic peers; (3) N400 or P600 component was measured to assess the semantic processing; (4) the incongruent condition minus the congruent condition or the unrelated condition minus the related condition was used to represent the different wave; (5) the time windows of N400 and P600 were 200–600 and 600–1000 ms, respectively.

Data extraction

Two reviewers (Danfeng Yuan and Xiangyun Yang) independently extracted and checked the data. Any

disagreement was resolved through discussion until a consensus was reached with the third reviewer (Zhanjiang Li). We extracted data from selected studies regarding the number of participants, mean age, diagnosis, verbal Intelligence Quotient (IQ), non-verbal IQ, full-scale IQ, receptive language ability, stimulus characteristics, Autism Quotient scores (AQ) as well as mean and standard deviation or F-value of effect sizes in each group. Five effect sizes were computed to examine the pattern of semantic processing in autistic individuals: N400 amplitude, N400 effect (the difference in the N400 amplitude between congruent and incongruent conditions), N400 amplitudes for congruent conditions, N400 amplitudes for incongruent conditions, and P600 amplitude. As words generally elicited a more centro-parietal N400 and pictures elicited a more frontally distributed N400, we mainly extracted N400 amplitude elicited by linguistic stimulus at centro-parietal sites and extracted N400 amplitude elicited by non-linguistic stimulus at frontal sites. A total of 14 articles were retained for the current meta-analysis. Among these, one study contained participants with two different age group and three studies had two different N400 time windows, each experiment was taken as an independent study, making a total of 18 datasets for meta-analysis.

Data synthesis

We divided N400 data into two categories according to the "stimulus types": linguistic and non-linguistic stimulus. Furthermore, paradigms of the semantic process were classified into three categories: semantic anomalies, semantic priming, and in-category and out-of-category words. The "N400 effect" and the "P600 effect" were defined as the amplitude difference between related and unrelated conditions or congruent and incongruent conditions. The statistical analysis was performed by Comprehensive Meta-Analysis 2.0 (CMA-Version 2 professional, Biostat Inc., Englewood, USA).

Statistical analysis

Hedge's g was calculated to correct for potential overestimation of the true effect in small study sample [28]. Hedge's g and 95% confidence interval (95% CI) were presented as effect sizes by the mean amplitude differences between the autistic and comparison groups, divided by the pooled standard deviations. When means and standard deviations were unavailable, the effect size was computed from F value or mean change scores with t or p-value within groups.

Heterogeneity between studies was examined by Cochran's Q and I^2 tests, which helps to evaluate the consistency across studies [29]. The pooled effect size were analyzed with a random-effects model when the heterogeneity was nonnegligible ($I^2 > 50\%$) or a fixed-effects model when the heterogeneity is acceptable ($I^2 \leq 50\%$).

The subgroup analysis and meta-regression were employed to explore potential sources of heterogeneity. The subgroup analysis categories were age, diagnosis, paradigm, modality, verbal level of the stimulus, and electrode site. The age was classified into two groups (children and adolescent, adults). The diagnosis was based on the DSM-IV and classified into Asperger syndrome and autism. As the N400 response can be elicited by several kinds of paradigms, we divided the paradigms into three groups (semantic priming, semantic anomalies, in-category and out-of-category words). Since the N400s are modality-dependent, we classified the studied according to modalities (auditory stimulus, visual stimulus, audiovisual stimulus). The studies' characteristics were divided into three groups based on the electrode site (Fz, Cz, Pz). Furthermore, according to the processing levels of the stimulus, the studies were classified into two groups (word level, sentence level). The meta-regression was performed with gender, verbal IQ, performance/non-verbal IQ, full-scale IQ, receptive language proficiency, Autism Quotient scores, and trials of each condition.

A funnel plot was conducted to detect whether the included studies had publication bias. The funnel plot was examined visually when the pool studies reached 10 [30]. A more symmetrical funnel shape indicates less bias between studies. To quantify the extent of asymmetry of the plot, we also applied the Egger test to check the publication bias [31].

Results

A total of 157 primary literature related to search protocol were discovered: 42 from PubMed, 81 from Web of Science and 34 from Embase. After selecting titles and abstracts, the full texts of 30 were considered potentially relevant. In the end, 14 articles were included in the meta-analysis after excluding 16 articles for the following reason: data no available, no case-control study, and no semantically related condition. The flowchart of study selection and inclusion is shown in Fig. 1.

The characteristics of the included studies are listed in Table 1. All of the studies were conducted between 2005 and 2022. In total, this meta-analysis pooled results from 254 autistic people and 262 neurotypical controls, in which half of the subjects were children and adolescents and half were adults. Most of the studies included in the meta-analysis enrolled autistic people without intellectual disability. Two studies recruited subjects with Asperger syndrome. In one study, autistic children with minimally verbal were recruited. There are two kinds of stimuli in the studies including verbal materials and visual materials. According to the "stimulus characteristics", articles were divided into two categories (linguistic and non-linguistic stimuli).

ERP component elicited by linguistic stimulus

In 14 articles and 18 studies, the N400 and P600 were elicited by linguistic stimuli [18,21,22,32–42]. Among the linguistic stimuli, some were presented with sentence in the semantic anomalies paradigm; the others were presented with words in the semantic priming paradigm or in-category and out-of-category words paradigm. Five effect sizes were computed to examine the N400 and P600 responses under the linguistic stimulus, including N400 amplitude, N400 different wave, N400 amplitude in congruent condition, N400 amplitude in incongruent condition, and P600 amplitude.

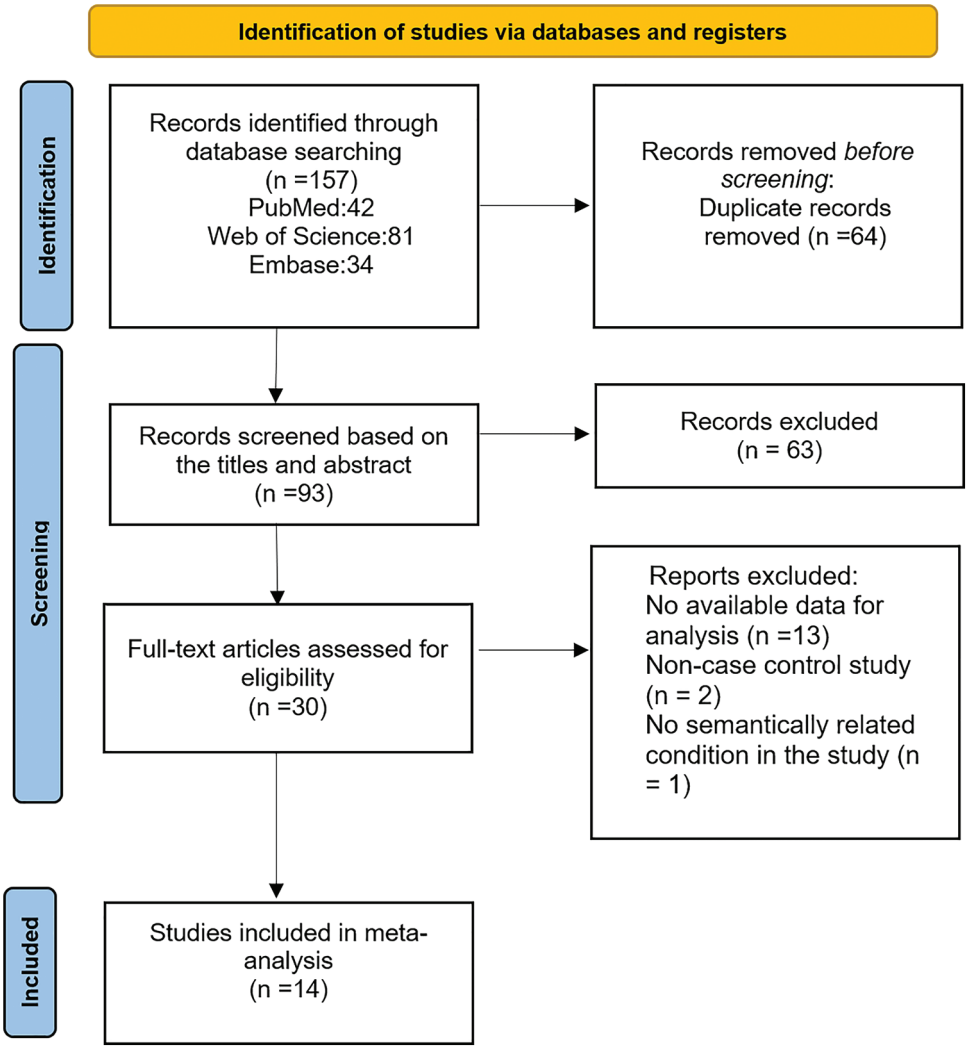


FIGURE 1. Flowchart of the study's inclusion and exclusion criteria.

TABLE 1

Characteristics of participants in ASD and control groups

Study ID	Diagnosis	N (TD) Age	N (ASD) Age	M% (TD)	M% (ASD)	FIQ (ASD/ TD)	VIQ (ASD/ TD)	PIQ (ASD/ TD)	Target stimuli	Time window (ms)	Paradigm	modality
Márquez-García et al., 2022 [38]	HFA	37 9.3	15 10.8	59.5	73.3	95.7/ 109.6	NA	NA	Image	200–500 500–800	Semantic anomalies	Audio-visual
Ferguson et al., 2022 [35]	HFA	24 34.0	24 32.8	66.7	66.7	104/ 106	104/ 103	103/ 107	Word	300–400 400–500	Semantic anomalies	Visual
O'Rourke et al., 2021 [22]	HFA	20 25.2	20 27.8	NA	NA	NA	107/ 118	101/ 112	Word/picture	300–400 400–500	Semantic priming	Visual
Barzy et al., 2020 [32]	HFA	24 31.8	24 32.6	75	75	NA	105.46/ 101.46	112.75/ 102.29	Word	300–500	Semantic anomalies	Auditory
Manfredi et al., 2020 [37]	HFA	16 11.4	24 12.6	100	100	100/ 107	7.8/12	12.4/ 13.5	Word/panel	350–550 550–750	Semantic anomalies	Auditory
DiStefano et al., 2019 [42]	HFA	18 7.6	20 7.4	72.2	86.7	NA	75.97/ 118.28	86.52/ 115.11	Word	600–900	Semantic priming	Audio-visual
Coderre et al., 2018 [34]	HFA	20 34.0	20 33	80	80	NA	101/ 114	101/ 111	Word/panel	300–500 500–800	Semantic anomalies	Visual

(Continued)

Table 1 (continued)

Study ID	Diagnosis	N (TD) Age	N (ASD) Age	M% (TD)	M% (ASD)	FIQ (ASD/ TD)	VIQ (ASD/ TD)	PIQ (ASD/ TD)	Target stimuli	Time window (ms)	Paradigm	modality
Coderre et al., 2017 [21]	HFA	20 34.3	20 33.3	85	85	NA	100/ 115	99/112	Word/picture	200–400 400–600 600–800	Semantic priming	Visual
Cantiani et al., 2016 [33]	NV/MV	10 6.3	15 6.3	70	70	NA	NA	NA	Word	350–500	Semantic priming	Audio-visual
Ribeiro et al., 2013 [18]	HFA	13 14	13 13	100	100	93/112	92/109	96/114	Picture	250–430 600–900	Semantic anomalies	Audio-visual
Gold et al., 2010 [36]	AS	17 21.9	16 23.1	75	82.4	NA	105.8/ 106.8	NA	Word	380–430 600–1000	Semantic priming	Visual
McCleery et al., 2010 [39]	HFA	14 6.0	14 5.8	92.9	92.9	NA	99.8/ 120.2	108.1/ 113	Word/ environmental sound	300–500	Semantic priming	Audio-visual
Ring et al., 2006 [40]	AS	11 25.9	11 23	63.6	63.6	NA	NA	NA	Word	350–450	Semantic anomalies	Visual
Dunn et al., 2005 [41]	ASD	10 8.5	10 8.5	NA	NA	96/113	92/116	98/112	Word	353–653	Word frequency	Auditory
Dunn et al., 2005 [41]	ASD	8 10.5	8 10.5	NA	NA	93/109	92/111	95/105	Word	353–653	Word frequency	Auditory

Abbreviation: HFA: high functioning autism, NV: nonverbal; MV: minimally-verbal; VIQ: Verbal IQ, PIQ: Performance/nonverbal IQ, N: Number of studies, FIQ: Full-scale IQ, NA: Not available, M: Male.

The N400 amplitudes difference under linguistic stimulus

Thirteen articles and 17 studies compared N400 amplitude differences elicited by linguistic stimuli between autistic and nonautistic group [18,21,22,32–41]. The sample size of the two groups were 218 and 237, respectively. As the heterogeneity was acceptable, a fixed effect model was used for analysis (I^2 = 0.00%, Q = 12.614). The analysis revealed a significantly reduced overall N400 amplitude in response to linguistic stimuli in the autistic group (Hedges' g = 0.350, 95% CI ranged from 0.187 to 0.498, $p < 0.001$, Fig. 2). Further analysis with potential moderators was evaluated.

The subgroup analysis was conducted as we assumed that the age, paradigm, diagnosis, level of verbal stimuli, modality, and electrode location might affect the N400 amplitude. The synthetic results of N400 amplitude were homogeneous in different ages, diagnoses, modalities, language levels, and paradigms. However, no significant effect size were found in the subgroups of Asperger syndrome, in-versus out-of-category words paradigm and Pz electrode site (Table 2), suggesting that N400 amplitude was comparable in the in-versus out of category words paradigm, Asperger's syndrome and Pz electrode site subgroups between autistic and nonautistic people.

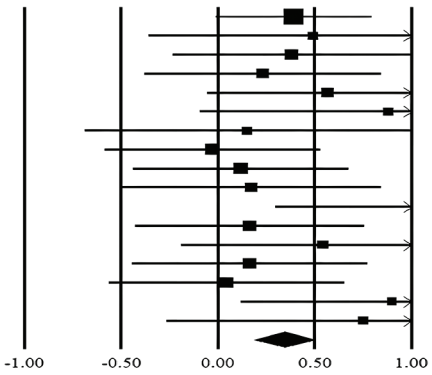
According to the meta-regression analysis, gender might be a potential moderator related to effect size (Z = 2.254, p = 0.024). The result suggested that with the increase of proportion of males in ASD group, the N400 amplitude showed a trend of decrease. However, age was not a potential moderator with nonsignificant effect size was found (Z = −1.358, p = 0.174). As the intellectual ability in autistic individuals, especially the language capacity, was highly heterogeneous, we considered "verbal IQ", "non-verbal IQ", "full-scale IQ", and "receptive language" as potential moderators that might affect the effect size. The result of moderator analysis showed that verbal IQ accounted for significant variance in the N400 amplitude (Z = −2.024, p = 0.043), which indicated that verbal IQ could significantly affect the N400 amplitude. However, the influence of non-verbal IQ and receptive language ability on N400 amplitude was not significant ($p < 0.05$). In addition, we considered that the trials under each condition and autistic traits measured by AQ might be the potential moderators. The results of moderator analysis revealed that these moderators were not significantly related to effect size ($p < 0.05$, Table 3). The funnel is symmetrical, indicating that publication bias was not captured among the smaller and larger studies (Fig. 3). The p-value of the Egger test was 0.064, which confirmed that the results did not suffer from publication bias.

N400 effect difference under linguistic stimulus

Among the articles, nine studies included a difference wave of N400 between incongruent and congruent conditions [22,33,35,36,38–40]. The fixed effect model was selected as insignificant heterogeneity (I^2 = 0.000%, Q = 1.751). After summarizing the outcome of N400 difference waves, the synthetic results revealed a marginally significant difference between the two groups (Hedges' g = 0.194, 95% CI ranged from −0.23 to 0.412, p = 0.08) (Fig. 2b). The subgroup analysis of the electrode site and diagnosis revealed that

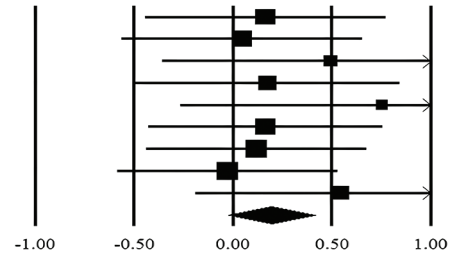
(a)

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Barzy et al.2020[32]	0.391	0.205	0.042	-0.012	0.793	1.904	0.057
Cantiani et al.2016[33]	0.492	0.435	0.190	-0.361	1.345	1.131	0.258
Coderre et al.2017 earlyN400[21]	0.381	0.313	0.098	-0.232	0.994	1.217	0.223
Coderre et al. 2017 lateN400[21]	0.230	0.311	0.097	-0.380	0.839	0.739	0.460
Coderre et al.2018[34]	0.566	0.316	0.100	-0.054	1.186	1.788	0.074
Dunn et al.2005 ge11-12[41]	0.880	0.498	0.248	-0.096	1.855	1.768	0.077
Dunn et al.2005 age8-9[41]	0.150	0.429	0.184	-0.691	0.991	0.350	0.726
Ferguson et al.2022 earlyN400[35]	-0.029	0.284	0.081	-0.586	0.527	-0.103	0.918
Ferguson et al.2022 lateN400[35]	0.118	0.284	0.081	-0.439	0.675	0.417	0.677
Gold et al.2010[36]	0.173	0.340	0.116	-0.495	0.840	0.507	0.612
Manfredi et al.2020[37]	1.043	0.381	0.145	0.297	1.789	2.740	0.006
Marquez et al.2022[38]	0.162	0.302	0.091	-0.430	0.754	0.537	0.591
McCleery et al.2010[39]	0.543	0.374	0.140	-0.190	1.276	1.451	0.147
O'Rourke et al.2021 earlyN400[22]	0.164	0.310	0.096	-0.445	0.773	0.528	0.597
O'Rourke et al.2021 lateN400[22]	0.044	0.310	0.096	-0.564	0.651	0.141	0.888
Ribeiro et al.2013[18]	0.899	0.400	0.160	0.115	1.682	2.248	0.025
Ring et al.2007[40]	0.752	0.520	0.271	-0.267	1.772	1.446	0.148
	0.342	0.080	0.006	0.187	0.498	4.307	0.000



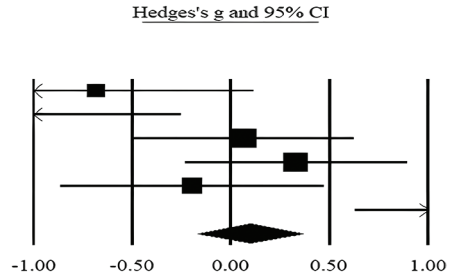
(b)

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
O'Rourke et al.2021 earlyN400[22]	0.164	0.310	0.096	-0.445	0.773	0.528	0.597
O'Rourke et al.2021 lateN400[22]	0.044	0.310	0.096	-0.564	0.651	0.141	0.888
Cantiani et al.2016[33]	0.492	0.435	0.190	-0.361	1.345	1.131	0.258
Gold et al.2010[36]	0.173	0.340	0.116	-0.495	0.840	0.507	0.612
Ring et al.2007[40]	0.752	0.520	0.271	-0.267	1.772	1.446	0.148
Marquez et al.2022[38]	0.162	0.302	0.091	-0.430	0.754	0.537	0.591
Ferguson et al.2022 earlyN400[35]	0.118	0.284	0.081	-0.439	0.675	0.417	0.677
Ferguson et al.2022 lateN400[35]	-0.029	0.284	0.081	-0.586	0.527	-0.103	0.918
McCleery et al.2010[39]	0.543	0.374	0.140	-0.190	1.276	1.451	0.147
	0.194	0.111	0.012	-0.023	0.412	1.751	0.080



(c)

study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cantiani et al.2016[33]	-0.683	0.406	0.165	-1.480	0.113	-1.681	0.093
Ring et al.2007[40]	-1.125	0.444	0.197	-1.994	-0.255	-2.534	0.011
Ferguson et al.2022 earlyN400[35]	0.066	0.284	0.081	-0.491	0.622	0.232	0.817
Ferguson et al.2022 lateN400[35]	0.330	0.286	0.082	-0.230	0.891	1.155	0.248
Gold et al.2010[36]	-0.196	0.341	0.116	-0.864	0.471	-0.577	0.564
Marquez et al.2022[38]	1.268	0.326	0.106	0.629	1.908	3.889	0.000
	0.097	0.136	0.019	-0.170	0.365	0.715	0.475



(d)

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cantiani et al.2016[33]	-0.274	0.397	0.157	-1.052	0.503	-0.691	0.489
Ring et al.2007[40]	-0.207	0.411	0.169	-1.013	0.599	-0.503	0.615
Ferguson et al.2022 earlyN400[35]	0.099	0.284	0.081	-0.458	0.655	0.347	0.729
Ferguson et al.2022 lateN400[35]	0.438	0.287	0.083	-0.126	1.001	1.523	0.128
Gold et al.2010[36]	-0.017	0.340	0.115	-0.683	0.649	-0.049	0.961
Marquez et al.2022[38]	0.096	0.302	0.091	-0.495	0.687	0.318	0.750
	0.079	0.133	0.018	-0.182	0.340	0.594	0.552

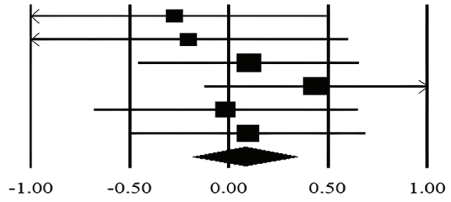


FIGURE 2. Forest plot of N400 amplitude for linguistic stimuli between ASD and controls.

neither of them would affect the heterogeneity, although the difference of N400 effect was more pronounced at the central electrode (Table 2).

Amplitudes of N400 in incongruent or congruent condition under linguistic stimulus

Five studies compared the N400 amplitude in congruent/related conditions between autistic and nonautistic groups [33,35,36,38,40]. The N400 amplitude under congruent condition of the two groups was comparable and the difference was statistically insignificant (Hedges' g = −0.017, 95% CI ranged from −0.632 to 0.597, p = 0.955, I2 = 80.454%, Q = 25.581) (Fig. 2c). Similarly, five studies included the N400 amplitude under incongruent/unrelated conditions. The difference was found to be insignificant and the studies in the pool were homogenous (Hedges'

TABLE 2

Results of N400 subgroup analyses

Moderators	Subgroup	N	Point estimate	Z-value	*p*-value	Q-value	I2 (%)
N400 amplitude		17	0.342**	4.307	0.000	12.614	0.000
Age group	Child/adolescent	7	0.553**	3.786	0.000	5.832	0.000
	Adult	10	0.256**	2.040	0.007	3.494	0.000
Paradigm	Semantic priming	7	0.263*	2.075	0.038	1.662	0.000
	Semantic anomalies	8	0.387**	3.113	0.002	8.872	21.100
	Word frequency	2	0.461	1.420	0.156	1.233	18.908
Diagnosis	ASD	15	0.342**	3.761	0.000	11.687	0.000
	AS	2	0.347	1.216	0.224	0.869	0.000
Level of verbal stimuli	Lexical	9	0.289*	2.449	0.014	3.219	0.000
	Sentence	8	0.387**	3.113	0.002	8.872	22.608
Modality	Auditory	4	0.520**	2.858	0.001	2.858	0.000
	Visual	9	0.220*	2.182	0.039	3.818	0.000
	Audiovisual	4	0.468*	2.549	0.011	2.231	0.000
Site	Fz	4	0.171	1.101	0.711	1.377	0.000
	Cz	6	0.267	1.907	0.057	4.861	0.000
	Pz	5	0.135	0.922	0.357	5.395	25.860
N400 effect		9	0.194	1.751	0.080	1.751	0.000
Site	Fz	4	0.171	1.101	0.711	1.377	0.000
	Cz	5	0.179	1.195	0.232	2.012	0.000
	Pz	4	0.106	0.680	0.497	5.140	41.635
Diagnosis	ASD	7	0.167	1.387	0.165	2.233	0.000
	AS	2	0.347	1.216	0.224	0.869	0.000
Congruent condition		6	−0.017	−0.056	0.955	25.581	80.454
Site	Fz	4	0.034	0.300	0.375	10.383	71.106
	Cz	5	0.011	0.029	0.977	24.694	83.802
	Pz	4	0.189	1.209	0.227	5.470	45.154
Incongruent condition		6	0.088	0.665	0.506	2.661	0.000
Site	Fz	4	0.236	1.515	0.130	2.988	0.000
	Cz	5	0.097	0.667	0.505	2.828	0.000
	Pz	4	0.269	1.726	0.084	2.292	0.000
Diagnosis	ASD	4	0.139	0.901	0.367	2.207	0.000
	AS	2	−0.057	−0.219	0.826	0.035	0.000

Abbreviation: N number of studies, Q test of heterogeneity, *p*-value, ASD Autism spectrum disorder, AS Asperger syndrome, *$p < 0.05$, **$p < 0.01$.

TABLE 3

Results of meta-regressions

	N	Point estimate	Lower limit	Upper limit	Z-value	*p*-value
N400 amplitude for linguistic stimuli						
Age	17	−0.010	−0.025	0.005	−1.358	0.174
Gender	12	0.019*	0.003	0.036	2.254	0.024
VIQ	14	−1.735*	−3.416	−0.055	−2.024	0.043
PIQ	13	−3.090	−8.290	2.260	−1.120	0.779
FIQ	8	−2.923	−7.093	1.248	−1.374	0.170
Receptive language	7	−3.977	−9.587	1.634	−1.389	0.165

(Continued)

Table 3 (continued)

	N	Point estimate	Lower limit	Upper limit	Z-value	*p*-value
Trials	17	0.001	−0.004	0.006	0.304	0.761
AQ	7	−0.142	−0.334	0.050	−1.449	0.147
P600 amplitude for non-linguistic stimuli						
Age	7	0.002	−0.019	0.023	0.182	0.855
VIQ	6	0.411	−0.655	1.479	0.755	0.450
PIQ	6	0.768	−0.555	2.093	1.138	0.255
Receptive language	5	0.342	−0.858	1.534	0.558	0.576

Abbreviation: N number of studies, VIQ = Verbal IQ, PIQ Performance/Nonverbal IQ, FIQ Full-scale IQ, *$p < 0.05$, **$p < 0.01$.

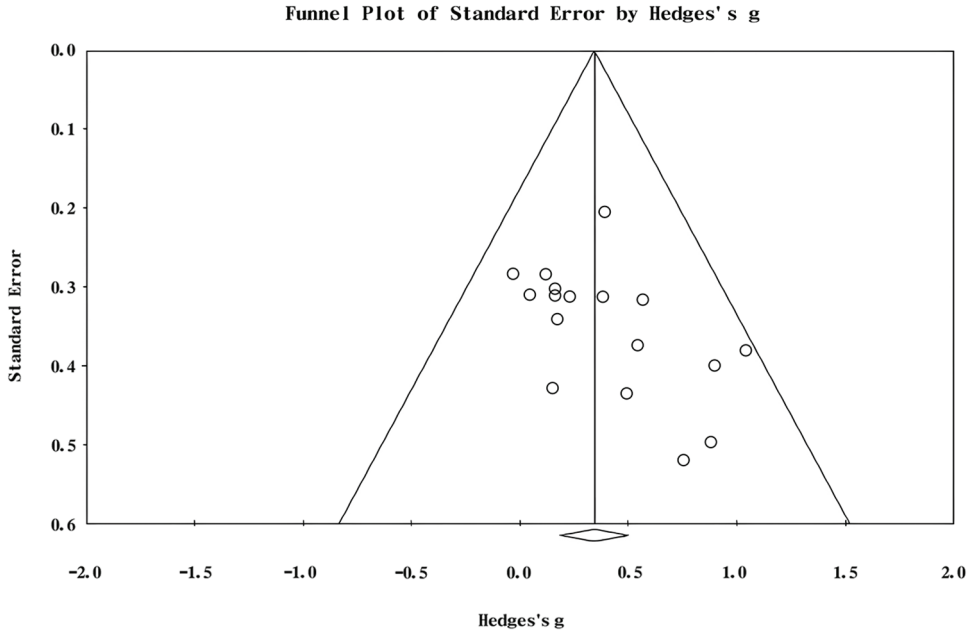


FIGURE 3. Funnel plot for publication bias of N400 amplitude for linguistic stimuli between ASD and controls.

g = 0.079, 95% CI ranged from −0.182 to 0.340, p = 0.552, I2 = 0.000%, Q = 2.922) (Fig. 2d). The subgroup analysis of the electrode site indicated a more negative N400 amplitude in incongruent and congruent conditions at the parietal site, although the effect sizes were insignificant (Table 2).

P600 amplitude difference under linguistic stimulus

We included 7 articles and 8 studies in the meta-analysis that reported P600 amplitudes differences between autistic and nonautistic group [18,21,22,34,37,38,42]. According to the no statistical heterogeneity for the P600 amplitude under speech sound stimulation, the fixed effect model was applied for analysis (Q = 12.516, I^2 = 44.073). Among the 8 studies, only 2 studies [21,38] revealed a late positive potential and 6 studies reported a sustained negativity [18,22,34,37,42]. The difference of P600 amplitude between two groups was significant, indicating greater negativity was elicited in the nonautistic group compared to the autistic group (Hedges' g = 0.289, 95% CI ranged from 0.059 to 0.518, p = 0.014, Fig. 4). As indicated by meta-regression, neither age nor intellectual ability showed a moderating effect ($p > 0.05$, Table 3).

ERP component elicited by non-linguistic stimulus

In a total of 5 article and 7 studies, non-linguistic stimuli such as music, pictures, and comics were applied to elicit N400 and P600 amplitudes [18,21,22,34,39]. Two effect sizes were computed to examine the response of non-linguistic stimulus: N400 amplitude and P600 amplitude.

N400 amplitude difference under non-linguistic stimulus

In a total of 5 articles and 7 studies, non-linguistic stimuli were applied to elicit N400 amplitude [18,21,22,34,39]. The available evidence was not enough to show a statistically significant difference between two groups in amplitudes of the N400 elicited by the non-linguistic stimuli (Hedges' g = 0.025, 95% CI ranged from −0.217 to 0.268, p = 0.837, Fig. 5). The studies in the pool were homogenous (I^2 = 23.510%, Q = 7.844).

P600 amplitude difference under non-linguistic stimulus

A total of 4 studies reported P600 amplitude difference under non-linguistic materials, the heterogeneity between studies was significant, and the random effect model was used for analysis (Q = 11.207, I^2 = 73.231) [18,21,22,34]. The pooled

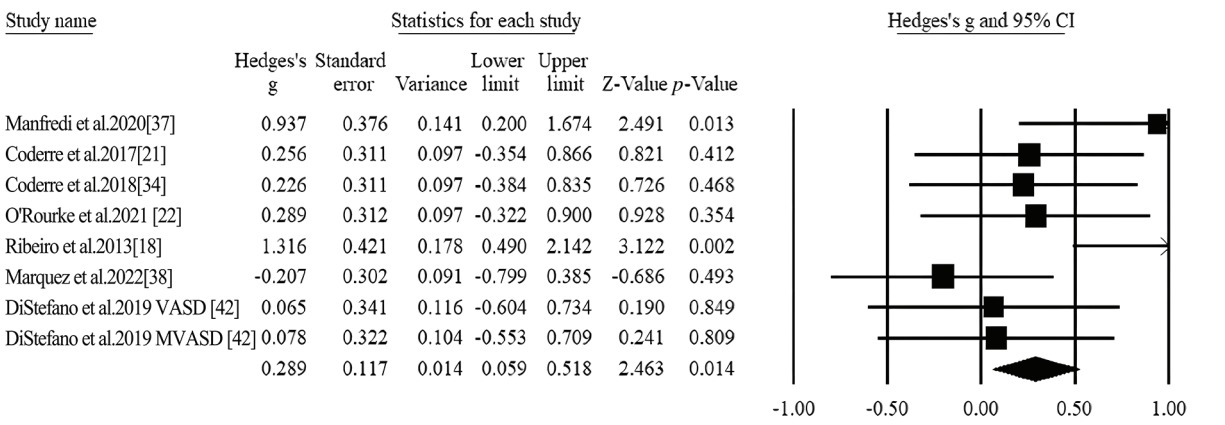


FIGURE 4. Forest plot of P600 amplitude for linguistic stimuli between ASD and controls.

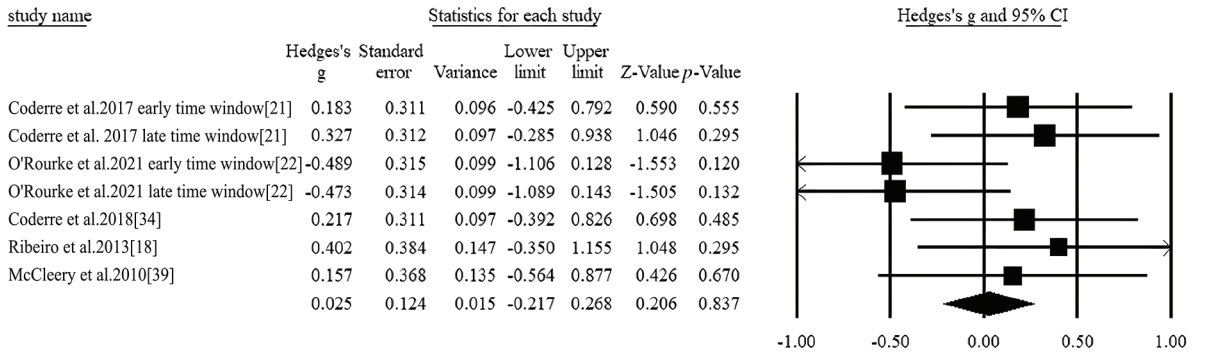


FIGURE 5. Forest plot of N400 amplitude for non-linguistic stimuli between ASD and controls.

result showed that no significant difference between the autistic individuals and comparison group was found (Hedges' g = −0.099, 95% CI ranged from −0.732 to 0.533, p = 0.271, Fig. 6).

Discussion

This is the first meta-analysis examining semantic processing in autistic individuals from the ERPs perspective and providing a comprehensive overview of current knowledge about language-related ERPs in individuals of ASD. The meta-analysis pooled the results of 18 studies and showed that the autistic people tend to display a reduced overall N400 amplitude and N400 effect compared to nonautistic people. Besides, the reduced N400 amplitude is limited to linguistic materials and no statistically significant difference was observed under non-linguistic stimuli, indicating a language-specific deficit of semantic processing in autistic individuals.

N400 is a well-studied ERP component of semantic processing [10]. Our meta-analysis revealed an overall reduced N400 amplitude in the autistic group, which suggests an abnormal semantic processing in autistic individuals. According to the assumption of weak central coherence theory, autistic individuals only focus on fine-grained detail and have difficulty integrating information within the linguistic context [43]. Studies of functional magnetic resonance imaging (fMRI) and intracranial recordings have revealed that the posterior temporal cortex, anterior temporal cortex, and inferior frontal cortex play a role in the semantic processing of linguistic [9]. The evidence from fMRI studies also supported that there is inefficient activation of the brain areas associated with semantic processing in autistic individuals [44].

The N400 effect is the difference wave between congruent and incongruent conditions. Previous studies have shown that the N400 effect is sensitive to individual's comprehensive skills [45]. In our meta-analysis, a reduced

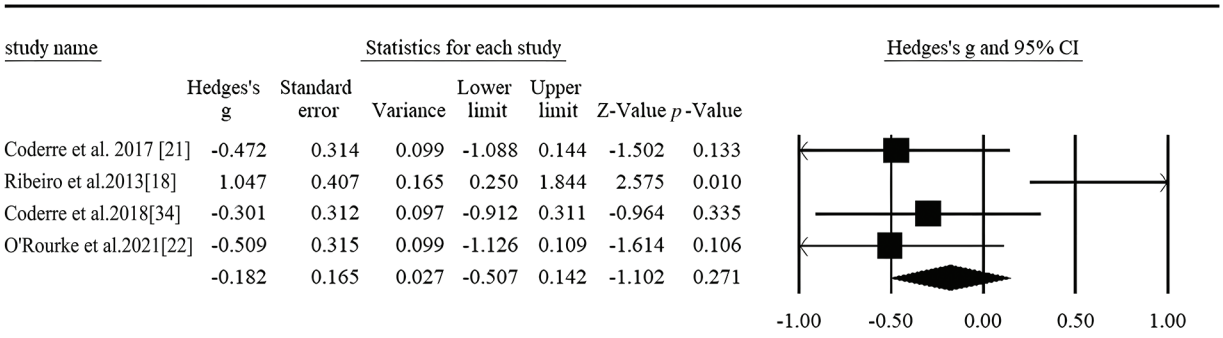


FIGURE 6. Forest plot of P600 amplitude for non-linguistic stimuli between ASD and controls.

N400 effect was found in autistic individuals, which suggests a possible developmental disability of semantic processing in autistic individuals. Although no significant difference between two groups was found in incongruous or congruous conditions, autistic individuals showed a subtle reduced N400 amplitude in the incongruous conditions and enhanced negativity in the congruous condition. This trend could be the result of a reduced N400 effect in the autistic group. Attenuated N400 under incongruent condition indicates a decreased activation of the incongruent context in autistic individuals, and the enhanced N400 in congruent condition reflects the difficulty in using context to generate expectancies in autistic individuals [46].

In addition, there is a contentious debate on whether the impairment of semantic integration in autistic individuals is a language-specific or a global impairment. The synthesized result of our meta-analysis suggested a language-specific deficit, which can also be supported by the fMRI analysis indicating that individuals of ASD rely more on visual processing in the occipital cortex than verbal processing in the temporal cortex [44,47]. Some researchers speculated that pictorial semantic processing is superior to verbal semantic processing in ASD [23]. As the fundamental role of perception processing in language development, perception deficits are closely related to language ability. The ERP study of speech-specific perception deficits in ASD also supported the result of our meta-analysis [48].

Furthermore, the results of meta-regression revealed that the effect size of N400 amplitude might be affected by the verbal IQ, indicating the difference of N400 amplitude between two groups is negatively related to language capacity. A similar finding could also be observed in subgroup analysis. For people diagnosed with Asperger syndrome, a part of family of ASD that preserved cognitive and verbal facilities, the difference of N400 amplitude was comparable. The result is consistent with the literature reported previously that N400 had a solid relationship to vocabulary learning in children and sentence comprehension in adults [49]. Furthermore, gender may be another potential moderator affecting the N400 amplitude. The result may be explained by the fact that better linguistic abilities are more common in females than in males [50]. The group differences of N400 response were observed in semantic anomalies and semantic priming paradigms, which suggests the possible difficulty in integrating semantic context and facilitating lexical access in autistic individuals [9]. However, the inverted-out-of-category words task showed no significant difference between the two groups, which means that the lexical frequency effect is less sensitive in distinguishing autistic from the nonautistic group.

The P600 is a positive deflection of compositional semantic integration processes [51]. The P600 effect can be observed in responses to syntactic violations, semantic incongruency, and pragmatic anomalies. Some studies reported that P600 was not specifically related to the language process but was more likely to reflect a general monitoring process and modulated with instructions [52]. According to our meta-analysis from limited literature, contrary to Pijnacker et al. [53], the comparison group showed significantly greater negativity than autistic individuals under linguistic stimuli. One possible reason is that the effect of P600 overlapped by the sustained anterior negativity. Previous findings have reported that the sustained anterior negativity could be explained by the increased demands on working memory load and the decreased monitoring of violations. Therefore, the presence of negativity masked the expected P600 effect of plausibility [54]. In addition, language capacity did not affect the P600 component according to the result of meta-regression. These results indicated that P600 might not be a stable index of semantic processing in ASD, even though a significant difference was detected between the two groups. Further research is needed to explore the potential role of P600 in ASD. In the contrary, the attenuated amplitude of N400 might be a reliable component that related to the poor semantic ability in ASD. More work is needed to address whether N400 has the potential to be a marker of language impairment in ASD.

Limitations

Our meta-analysis contains some limitations. First, only a few studies recruited autistic participants with minimally verbal ability [55]. The characteristic of N400 waveform in

individuals of ASD with intellectual disability should be further explored. Second, the number of studies was relatively limited. Some researches were excluded from this study because no N400 response was elicited. Third, given that the amplitude response of N400 was most susceptible to manipulation and the latency was generally stable [10], only a limited number of studies reported the N400 latency. Therefore, our meta-analysis only incorporated the N400 amplitude index and did not include the latency indicators. Last but not least, as much of the literature reported previously, the ASD group shows atypical lateralization patterns of ERPs to speech stimuli [56]. The relationship between cerebral lateralization and language-related ERPs in autistic individuals should be considered in future studies.

Conclusion

This meta-analysis indicates an overall pattern of a reduced N400 amplitude and difference wave in autistic people under linguistic stimuli. The N400 amplitude is modulated by verbal intelligence and gender. In conclusion, our findings suggest a language-specific semantic processing deficiency in autistic people from some aspects of neurocognitive functions. The decrease of N400 amplitude might be a promising indication of poor language capacity in ASD.

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Availability of Data and Materials: All data generated or analysed during this study are included in this published article, and its supplementary information files.

Ethics Approval: None.

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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Supplementary Materials

TABLE S1

Search strategies

Database	Retrieval
Pubmed	((((((“Autism Spectrum Disorder”[Mesh]) OR (Asperger Syndrome[Title/Abstract])) OR (Autistic disorder[Title/Abstract])) OR (Autistic Spectrum Disorder[Title/Abstract])) OR (Disorder, Autistic Spectrum[Title/Abstract])) AND ((((“Semantics”[Mesh]) OR (Semantic[Title/Abstract])) OR (Language[Title/Abstract])) OR (Linguistics[Title/Abstract]))) AND (((((Event Related Potential[Title/Abstract]) OR (N400[Title/Abstract])) OR (P600[Title/Abstract])) OR (Potential, Event-Related[Title/Abstract])) OR (Potential, Event Related[Title/Abstract]))
Web of science	#1 ((((TS = (Autism Spectrum Disorder)) OR AB = (Asperger Syndrome)) OR AB = (Autistic disorder)) OR AB = (Autistic Spectrum Disorder)) OR AB = (Disorder, Autistic Spectrum)
	#2 ((((AB = (Event Related Potential)) OR AB = (N400)) OR AB = (P600)) OR AB = (Potential, Event-Related)) OR AB = (Potential, Event Related)
	#3 (((TS = (Semantics)) OR AB = (Semantic)) OR AB = (Language)) OR AB = (Linguistics)
	#1 AND #3 AND #2
Embase	#1 ‘autism spectrum disorder’: ab, ti OR ‘asperger syndrome’: ab, ti OR ‘autistic disorder’: ab, ti OR ‘autistic spectrum disorder’: ab, ti OR ‘disorder, autistic spectrum’: ab, ti
	#2 ‘event related potential’: ab,ti OR n400: ab, ti OR p600: ab, ti OR ‘potential, event-related’: ab, ti OR ‘potential, event related’: ab, ti
	#3 semantics: ab, ti OR semantic: ab, ti OR language: ab, ti OR linguistics: ab, ti
	#1 AND #3 AND #2