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Addiction as a brain disease? A meta-regression comparison of error-related brain potentials between addiction and neurological diseases

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ABSTRACT

The notion that addiction is a "brain disorder" is widespread. However, there is a lack of evidence on the degree of disorder in terms of error processing in addiction. The present meta-analysis aimed at shedding light on this by comparing error-processes with populations with well-recognized brain disorders. We included 17 addiction and 32 neurological disorder studies that compared error-related negativity (ERN) or error positivity (Pe) amplitudes/latencies between experimental and healthy-control groups. Meta-regression analyses were performed for the intergroup comparison and other moderators. Both diagnoses were accompanied by a diminished ERN amplitude, although the degree of impairment was marginally larger in neurological disorders. Neurological disorders presented shorter ERN latencies than addiction when compared with controls. The two groups did not differ in Pe amplitude/latency. Except for a reduced ERN amplitude found along with aging, no other moderator contributed significantly to divergent findings about these four ERP indexes. The results support the brain disease model of addiction, while stressing the importance of quantifying the degrees of brain dysfunctions as a next step.

1. Introduction

1.1. The debate about addiction as a brain disease

The question of whether addiction is a brain disease, first debated in Leshner's (1997) influential *Science* paper, has triggered considerable dispute ever since. The brain-disease model was built upon countless neuroimaging findings that indicated structural and functional brain differences between people with addictive disorders and healthy controls (Xiao et al., 2015). Accordingly, the term of 'brain disease' can be used interchangeably with 'brain disorder' in this case (not referring to examples of forms due to infection). For instance, drug or alcohol abuse was associated with brain structure changes, ranging from minor damage to neurons to severe brain injuries similar to neurological diseases such as traumatic brain injury (TBI), stroke, and multiple sclerosis (Bechara, 2005; Bechara et al., 2000; Goldstein et al., 2009; Volkow et al., 2004). This suggests that both addiction and neurological disorders are associated with brain disorders.

The main arguments of those who oppose this view are that the choice of using a substance was made by oneself, and one can recover possibly without treatment, which stands in sharp contrast to the causes and the possibilities for recovery associated with diseases that incur neurological damage (Satel and Lilienfeld, 2014). Accordingly, the neural dysfunction characteristic of addiction is insufficient for permanent impairment, thus countering the notion that addiction is best understood as a brain disease (Levy, 2013).

1.2. Analogy of addiction and neurological disorder in error-related processes

To shed new light on this debate, our present aim is to provide unique and robust evidence on the analogies and dissimilarities of brain dysfunction between addiction and other types of neurological disease, focusing in particular on the neural activities underlying error processing through a meta-analysis.

The rationale for comparing addiction and neurological disease regarding error-processing related neural activities includes but is not limited to: 1) brain regions involved in reinforcement learning (which capitalizes on calculating prediction error and using it to learn) were more or less impaired in addiction as well as neurological disease, such

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as the mesocorticolimbic dopamine reward pathway (Arias-Carrión et al., 2010; Navarri et al., 2022); 2) both addiction and neurological disease show post-mortem alterations in neurotransmitters (metabolism) involved in error monitoring (e.g., Dopamine, Norepinephrine, Serotonin, GABA; Jocham and Ullsperger, 2009) and in the frontal cortex (Cadet et al., 2014; Goldstein et al., 2011; Gramage and Herradon, 2011; Kärkkäinen et al., 2021; Reinikainen et al., 1988); 3) the existence of bidirectional interactive relationships between addiction and neurological disease (for instance, a substantial proportion of TBI occurs in intoxicated individuals, and TBI can serve as a risk factor for alcohol use disorder; Weil et al., 2018). Notably, we did not aim to verify addiction and neurological disease are the same thing, or they are comparable, but to gauge the degree of brain disorder in terms of error processing in addiction by comparing it with a population with well-recognized brain disorders.

1.3. Error processing

Error processing refers to the ability to detect errors and evaluate performance, which is considered a fundamental aspect of cognitive control that allows for flexible behavior modification to optimize future decisions (Desender et al., 2021; Ridderinkhof et al., 2004). This aspect is of particular relevance in the clinical context, as self-control failure (Krönke et al., 2018) and maladaptive behavior (i.e., post-error adaptation, Wessel, 2018) - which are salient characteristics of error processing - have been previously reported in patients with addiction (Inzlicht et al., 2015; Kotabe and Hofmann, 2015; Luijten et al., 2014) as well as neurological disorders (Lenzoni et al., 2022; Pezzetta et al., 2021).

Dysfunctional error monitoring may be observed at the behavioral level and as modulation of error-related brain responses or oscillatory activity. In normal conditions, error commission robustly elicits two event-related potentials (ERPs) components: an early component, known as error-related negativity (Ne or ERN), and a late component, termed error positivity (Pe). ERN is a frontocentral negativity occurring 50–150 ms after an incorrect response, signaling the commission of error (Coles et al., 2001; O'Connell et al., 2007). Source localization analysis indicated that the ERN originated from the posterior medial frontal cortex (pMFC) and anterior cingulate cortex (ACC) (Holroyd et al., 2004; Veen and Carter, 2002). A correct response can trigger a similar component, namely correct-response negativity (CRN). The difference wave (i.e., delta score, ERN − CRN) was also used in some studies as the index of performance monitoring (Gorka et al., 2019). Pe is a positive wave that can be recorded 200–500 ms after the error over centro-parietal regions (Falkenstein et al., 2000), and has been proposed to represent error awareness (Leuthold and Sommer, 1999; Overbeek et al., 2005) and motivational salience of an error (Falkenstein et al., 2000; Ridderinkhof et al., 2009). A recent study indicates that instead of signaling the consciousness of an error directly, Pe reflects the trajectory of evidence accumulation after a decision, and such accumulation terminates when the agency realizes the mistake (Desender et al., 2021). Contrary to ERN, the source of Pe remains equivocal, with studies showing it arises from activity in the parietal cortex (O'Connell et al., 2007), rostral ACC (rACC; Herrmann et al., 2004; van Boxtel et al., 2005), anterior insula (Harsay et al., 2012), and prefrontal cortex (Masina et al., 2019).

1.4. Error processing and addiction/neurological disorders

To date, four reviews/meta-analyses have summarized ERN and Pe findings in addiction research (systematic review: Luijten et al., 2014; meta-analysis: Lutz et al., 2021; Pasion and Barbosa, 2019; Zhang et al., 2021). Pasion and Barbosa (2019) and Zhang et al. (2021) found that ERN amplitude did not differ significantly between substance users and healthy controls. In contrast, Lutz et al. (2021) showed that the severity of addiction matters, such that only those diagnosed with substance use disorder present a significant reduction of ERN amplitude. Only two of these reviews examined Pe, and found no apparent difference between the substance use group and the healthy controls (Luijten et al., 2014; Lutz et al., 2021). With a few exceptions (e.g., Lutz et al., 2021), in most of these meta-analyses, effect size dependency was not yet handled in accordance with recent methodological advances (Pustejovsky and Tipton, 2022). There are numerous sources of dependency, either between studies (e.g., studies from the same research group) or within the study (e.g., a study reported multiple outcomes). For studies that provided more than one effect size, researchers selected the value they predetermined (e.g., use data from certain electrode(s) for ERN scoring), or halved the sample size of the control group when there were two experimental groups and then treated the two effect sizes as if they were from different studies. Such practices may result in hampered moderation analyses and compromised aggregated effect size estimation accuracy (Scammacca et al., 2014). Furthermore, only two of the four reviews reported results on Pe. ERN and Pe show more dissociation than associations (Di Gregorio et al., 2018; see review: Overbeek et al., 2005), and substance use may be accompanied by aberrant ERN but intact Pe, or vice versa.

As for neurological diseases, there are three relevant systematic reviews summarizing ERN and Pe findings (Lenzoni et al., 2022; Pezzetta et al., 2021; Pyasik et al., 2022). It was found that for most of the neurological patient groups, ERN amplitude was reduced, whereas Pe was unabated when compared to healthy controls (Pezzetta et al., 2021), suggesting distinct patterns for the processes underlying these two error-related potentials. However, the overall effect size of error-related mechanisms in neurological patients has not been quantitatively evaluated via a meta-analysis.

1.5. The present study

The neural basis of error processing is among the most adequately studied fields for both addiction and neurological disease. However, so far, no study has investigated and quantified whether and how these populations share a similar impairment in the functional mechanisms of error processing - in line with the brain disease model - or whether addiction and neurological diseases can be considered functionally distinct. This study aimed to shed new light on the debate of 'addiction as a brain disease' through intergroup comparisons of neural activities (i.e., ERN and Pe) underlying error processing via meta-analyses. Based on the overview above, we expect both groups to show similar patterns of error-related brain response deficits, but the degree of impairment is larger in neurological disorders. Thus, in the present unregistered meta-analysis, we examined the role of Group (addiction vs. neurological disease) as a focal moderator that may explain between-study heterogeneity.

As a secondary focal moderator, we included the effect of Age. The relationship between ERN (or Pe) amplitude and age may be an inverted U-shaped curve, such that it peaks in young adults (Boen et al., 2022), and then declines due to the degradation of the mesocorticolimbic DA-system during normal aging (Beste et al., 2009).

In addition, we examined several parity moderators, including medicine (Seer et al., 2017; Stemmer et al., 2007) and task (Pasion and Barbosa, 2019; Vallet et al., 2021) since discrepancies exist concerning their role in ERN and Pe. As to certain other potential parity moderators, robust evidence for their moderating effects is still lacking (e.g., ERN peaking score: delta vs. error-related; electrode analyzed; the percentage of males), and we therefore examined their roles in exploratory analyses.

2. Methods

This review has been reported following the Preferred Reporting Items for Systematic Review and Meta-analysis (Page et al., 2021).

2.1. Literature search and screening

Literature searches were carried out separately for addiction and neurological disease. For addiction, 6 databases (Medline, PsycINFO, Embase, CINAHL, Web of Science, and Scopus) were searched until October 5th, 2021. Search terms and synonyms indicating substance use (e.g., alcohol, amphetamine, cocaine, cannabis, heroin, ketamine, methamphetamine, benzodiazepines) were combined with terms indicative of the ERP component (e.g., ERN, Pe). For neurological disease, an updated literature search was carried out based on RP's recent review (Pezzetta et al., 2021). Search strategies for all databases are available in the Supplementary Materials.

For addiction, the inclusion criteria were that the studies: (a) were presented in English and published in peer-reviewed journals; (b) were conducted on human participants; (c) assessed the amplitude and/or latency of ERN and/or Pe during error processing; (d) compared a group with current or past substance use (or a group diagnosed with the neurological disease) to a healthy control group, and each group had no less than 5 participants; (e) statistics reported in the paper or data provided by authors via contacts allowed effect size calculation. We excluded studies: (a) focused on the acute effect of substance use; (b) in which a pure substance use/neurological disease effect cannot be isolated (e.g., comorbid disorders such as depression, anxiety, etc.). For neurological disease, in line with Pezzetta et al. (2021), the search included the following neurological disorders: "Parkinson's disease", "multiple sclerosis", "spinal cord", "stroke", "brain damage", "lesion/s", "neurological", "mild cognitive impairment", "dementia", "Alzheimer", and "Huntington".

For addiction, a total of 174 articles were initially identified after deduplication. The title, abstract, and full text were double-blindly screened by YL and RP through Rayyan (Ouzzani et al., 2016). Conflicts were first addressed between the two raters, then the whole group for complicated ones. After title and abstract screening, there were 27 articles left, of which another 10 were excluded (see details in Fig. 1).

For neurological disease, the updated literature search (from 9/4/2020–5/10/2021) resulted in 22 new articles. Out of them, only one was finally included (Niessen et al., 2020). Another 31 studies from Pezzetta et al. (2021) met our inclusion criteria and were also included.

2.2. Quality assessment and data extraction

The Appraisal tool for Cross-Sectional Studies (AXIS) was used to assess the quality of included studies (Downes et al., 2016). It evaluates the quality of a study in terms of study aim declaration, sample size justification, study design and measurements appropriateness, results reporting sufficiency, significance justification, inference from the results to the conclusions, limitations, and ethics. Items 13, 14, and 19 were deleted as they were inappropriate for the present aim. Each item was rated with 'Yes' or 'No'. The overall quality of a study was represented by the percentage of 'Yes' answers. YL and FM assessed the quality independently, and the agreement was high (93.37%, 732/784).

Information coded mainly includes those used to calculate the effect size and its variance, as well as moderators examined in the meta-regression analyses. Some other important study characteristics were also coded and presented in Tables 1a; 1b. Each paper was blindly coded by two authors (YL, RP, or FM).

2.3. Meta-Analytic Procedures

The analyses were conducted in the following steps: 1) effect size computation; 2) outlier detection and influence analysis; 3) overall effect size calculation; 4) heterogeneity test and moderator analysis; 5) small sample bias assessment. All analyses were performed separately for the four outcomes (ERN amplitude, Pe amplitude, ERN latency, and Pe latency) in R-4.1.0.

2.3.1. Effect size computation

The standardized mean difference Hedges' *g* was calculated since it

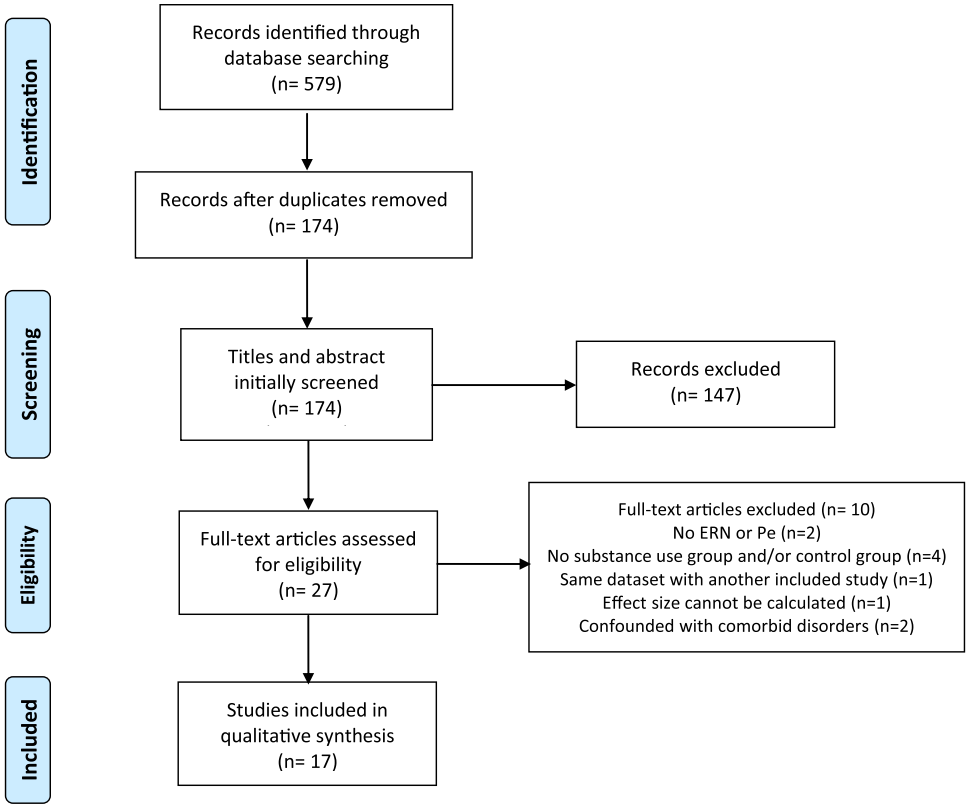

Fig. 1. PRISMA flowchart.

Table 1a
Characteristics of included studies (Addiction).

Study	Sample size (gender, age: mean±sd)	The sample size for ERN/Pe calculation	Education years (M±SD)	Substance	Duration of substance use/yrs	Severity	Measures	Poly-substance use/usage of other substance	Treatment	Treatment duration (month)	Abstinence duration	Medicine	Task	Reference	Baseline/ ms	Time window/ ms	Nr of electrode	Electrodes analyzed
Chen et al. (2013)	20SUG(M, 37.1 ± 9.5); 15CON(M, 32.5 ± 9.9)	17SUG; 15CON	SUG: 8.4 ± 3.0; CON: 13.7 ± 4.6	Heroin	12.4 ± 3.1	Clinical	DSM-IV	No	Yes	8.2 ± 2.0	NA	NA	Flanker	Average	NA	ERN: 0–100	32	ERN: Fz, Fcz, Cz
Franken et al. (2007)	14SUG(13 M, 38.1 ± 10.2); 13CON(8 M, 32.0 ± 13.8)	Same	Comparable, all had lower or intermediate education levels	Cocaine	NA	Clinical	DSM-IV	4 also used heroin	Yes	NA	1–13 months	NA	Flanker	Linked mastoids	-200–0	ERN: 25–75; Pe: 200–400	64	ERN: Fz, Fcz, Cz; Pe: FCZ, Cz, Pz
Franken et al. (2010)	23SUG(NA, 21.7 ± 2.7); 28CON(NA, 21.3 ± 2.8)	21SUG (11 M); 25CON (11 M)	NA	Tobacco	> 5 cigarettes/ day for one year	Subclinical	FTND	NA	No	NA	No abstain	NA	Flanker	Linked mastoids	-200–0	ERN: 25–100; Pe: 200–400	32	ERN & Pe: Fz, Cz, Pz;
Franken et al. (2017)	48SUG(25 M, 23.4 ± 10); 49CON(24 M, 22.9 ± 8.5)	44SUG; 43CON	Comparable, all follow higher education	Alcohol	NA	Subclinical	QFV	NA	No	No	No abstain	NA	Flanker	Linked mastoids	-100–0	ERN: 25–75; Pe: 200–400	32	ERN: Fz, Fcz, Cz; Pe: Cz, CPz, Pz
Fridberg et al. (2013)	30SUG(24 M, 20.20 ± 2.86), 32CON(20 M, 20.84 ± 2.95)	Same	SUG: 13.07 ± 1.28; CON: 13.97 ± 1.49	Cannabis	4.20 ± 3.71	Clinical	DSM-IV	No	No	No	2 days on average	No	Continuous performance task	Nose	-200–0	ERN: - 50–150; Pe: 100–450	37	ERN: FCz; Pe: CPz
Gorka et al. (2019)	39 current AUD(19 M, 23.3 ± 3.2); 60 remitted AUD(27 M, 23.2 ± 2.8); 43 at-risk for AUD(18 M, 22.4 ± 3.6); 53CON(21 M, 22.2 ± 2.5)	Same	NA	Alcohol	NA	Clinical: AUD; Subclinical: AUD in remission and high risk	DSM-5	Yes	No	No	only for the remission group	Some participants had	Flanker	Linked mastoids	-500∼ -300	ERN: 0–100	64 (sample 1) and 34 (sample 2)	ERN: Cz
Kim and Kim (2019)	25SUG(F, 21.44 ± 1.89); 25CON(F, 21.72 ± 2.44)	Same	SUG: 14.92 ± 1.00; CON: 15.20 ± 1.32	Alcohol	NA	Subclinical	AUDIT & AUQ	NA	No	No	No	NA	Flanker	Average	-100–0	ERN: 50–150; Pe: 150–400	64	ERN & Pe: Fz, FCZ, Cz & Pz
Lannoy et al. (2017)	20SUG(8 M, 20.25 ± 1.62); 20CON(7 M, 21.20 ± 2.59)	Same	Undergraduate students	Alcohol	NA	Subclinical	AUDIT & AUQ	No	No	No	No abstain	No	GNG	Average	-500–0	ERN: -50–80; Pe: 80–300	128	ERN & Pe: Cz, Fz, FCz
Luijten et al. (2011)	13SUG(9 M, 20.7 ± 1.3); 14CON(10 M, 21.4 ± 2.6)	Same	Undergraduate students	Tobacco	≥ 10 cig/day for two years	Subclinical: medium level of dependence	FTND	No	No	No	No abstain	No	Flanker	Linked mastoids	-200–0	ERN: 25–75; Pe: 250–350	34	ERN & Pe: FCz, Cz, CPz
Marhe et al. (2013)	49SUG (44 M,39.6 ± 8.4); 23CON(17 M, 39.9 ± 9.4)	Same	Comparable	Cocaine	12.2 ± 6.8	Clinical	DSM-IV	NA	No	No	the first week in detoxification treatment	No	Flanker	Linked mastoids	-100–0	ERN: 25–100;	32	ERN: Fz, FCz, Cz
Morie et al. (2014)	23SUG(16 M, 44.0 ± 6.6);	Same	SUG:12.5 ± 2.3; CON: 12.2 ± 1.4	Cocaine	NA	Clinical	DSM-IV	NA (potential:	NA(8 never get any treatment)	NA	3.9 days on average (1 day to 1 week)	No	GNG	Nasion	NA	ERN: 30–70;	168	ERN: FCz; Pe: CPz

(*continued on next page*)

Table 1a (*continued*)

Study	Sample size (gender, age: mean±sd)	The sample size for ERN/Pe calculation	Education years (M±SD)	Substance	Duration of substance use/yrs	Severity	Measures	Poly-substance use/usage of other substance	Treatment	Treatment duration (month)	Abstinence duration	Medicine	Task	Reference	Baseline/ ms	Time window/ ms	Nr of electrode	Electrodes analyzed
	27CON(20 M, 41 ± 8.5)							nicotine, alcohol)								Pe: 100–300		
Padilla et al. (2011)	14SUG(M, 37.86 ± 9.3); 14CON(M, 43.5 ± 14.5)	Same	SUG: 13.5 ± 2.2; CON: 16.07 ± 3.5;	Alcohol	NA	Clinical	DSM-IV	NA	NA	NA	Yes (1–4month)	No	Flanker	Linked mastoids	-200–100	ERN: 20–120	64	ERN: FCz
Rass et al. (2014)	22 daily smokers (13 M, 27.2 ± 5.3); 31 intermittent smokers (12 M, 23.9 ± 4.4); 30CON(14 M, 25.2 ± 4.3)	Flanker: 21 daily smokers; 26 intermittent smokers; 25 controls GNG: 21 daily smokers; 29 intermittent smokers; 26 controls	Daily smokers:14.8 ± 1.6; Intermittent smokers: 15.8 ± 1.6; CON: 16.6 ± 2.0	Tobacco	Daily smokers: 9.4 ± 6.4; Intermittent smokers: 5.6 ± 4.4	Subclinical	FTND	No	No	No	No abstain	No	Flanker & GNG	Nose	-200–0	ERN: -50–100; Pe: 100–250	34	ERN: FCz; Pe: Cz
Smith et al. (2015)-female	15SUG(F, 21.0 ± 2.3); 17CON(F, 21.4 ± 2.0)	Same	NA	Alcohol	Regular drinking: 3.9 ± 2.8	Subclinical	AUDIT	Cannabis	No	No	No	NA	Flanker	Linked mastoids	-500–0	ERN: 0–150	58	ERN: Fz
Smith et al. (2015)-male	16SUG(M, 23.0 ± 2.2); 18CON(M, 22.1 ± 2.4)	Same	NA	Alcohol	Regular drinking: 6.3 ± 3.1	Subclinical	AUDIT	Cannabis	No	No	No	NA	Flanker	Linked mastoids	-500–0	ERN: 0–150	58	ERN: Fz
Smith et al. (2016)-female	13SUG(F, 20.0 ± 1.2); 17CON(F, 20.1 ± 1.2)	Same	NA	Alcohol	NA	Subclinical	AUDIT	No	No	No	No	No	Stop task	Linked mastoids	-500–0	ERN: 0–250	58	ERN: Fz
Smith et al. (2016)-male	21SUG(M, 19.8 ± 1.2); 20CON(M, 20.1 ± 1.1)	Same	NA	Alcohol	NA	Subclinical	AUDIT	No	No	No	No	No	Stop task	Linked mastoids	-500–0	ERN: 0–250	58	ERN: Fz
Smith et al. (2017)-aware	25SUG(12 M, 22.2 ± 2.5); 35CON(18 M, 21.8 ± 2.2)	Same	NA	Alcohol	NA	Subclinical	AUDIT	No(only tobacco)	No	No	No	No	Error awareness task	Linked mastoids	-200–0	ERN: 0–120; Pe: 300–500	58	ERN: FCz; Pe: CPz
Smith et al. (2017)-unaware	16SUG(8 M, 22.0 ± 2.8); 13CON(6 M, 21.0 ± 1.6)	Same	NA	Alcohol	NA	Subclinical	AUDIT	No(only tobacco)	No	No	No	No	Error awareness task	Linked mastoids	-200–0	ERN: 0–120; Pe: 300–500	58	ERN: FCz; Pe: CPz
Sokhadze et al. (2008)	19 SUG(12 M, 42.1 ± 5.5); 15 CON(7 M, 37 ± 9.4)	6SUG(4 M, 42.11 ± 5.60); 6CON(3 M, 39.07 ± 9.48)	NA	Cocaine	NA	Clinical	DSM-IV	Cannabis, tobacco	No	No	< 2 months	No	GNG	Average	-700~ -500	ERN: 50–200	128	ERN: Fz, Afz, F1, F2

Note. NA: not available; Gender: M: all are males, F: all are females, X: mixed (the specific number for males and females was coded if it was reported, e.g., 17 M); SUG: substance use group. CON: control group; AUD: alcohol use disorder; DSM: Diagnostic and Statistical Manual of Mental Disorders; AUDIT: Alcohol Use Disorder Identification Test; FTND: Fagerstrom Test for Nicotine Dependence; QFV: Quantity-Frequency-Variability index; AUQ: Alcohol Use Questionnaire

corrects for small study bias (Hedges, 1981). Hedges' *g* and its variance were calculated from *M*(*SD*) of the experimental group (addiction/-neurological disease) and the control group by the escalc() function ('metafor' package, Viechtbauer, 2010). When *M* and/or *SD* were unavailable, the corresponding *t*-test or *F*-test result was used, and Hedges' *g* was calculated by the 'esc' package (Lüdecke and Lüdecke, 2019). For ERN amplitude, a positive Hedge's *g* indicates lower amplitude (i.e., less negative values) in the experimental group, since its polarity is negative; for Pe amplitude, ERN latency, and Pe latency, a positive Hedge's *g* indicates enlarged amplitude/delayed latency in the experimental group.

2.3.2. Outlier detection and influence analysis

Studentized residuals and Cook's distance were used to detect outliers and influential cases (Berres and Erdfelder, 2021). Since these methods were not available for models with Robust Variance Estimation (RVE), they were applied to a randomized multilevel model without RVE. Effect size with a z score outside of ± 1.96 was deemed an outlier, and when its Cook's distance value was larger than 4/N (N being the number of effect sizes), it was considered an influential case.

2.3.3. Overall effect size calculation

Many studies contributed more than one effect size, including results from different electrodes, different tasks, multiple experimental groups, medicine on/off, etc. To account for effect size dependency, the correlated and hierarchical effects (CHE) model considers both correlated (e.g., effect sizes from the same study) and hierarchical (e.g., effect sizes from the same lab across studies) effects using the RVE methods (Pustejovsky and Tipton, 2022) was built by the 'metafor' (Viechtbauer, 2010) and 'clubSandwich' packages (Pustejovsky, 2022). The correlation of within-study effect sizes was set to 0.6, and the robustness of the results was examined through sensitivity tests by varying the coefficient from 0 to 1.

2.3.4. Heterogeneity test and moderator analysis

We estimated the heterogeneity using the Q test, τ (*SD* of the distribution of true effects), and I^2 (proportion of true heterogeneity to the total variance of observed effects). In general, a significant Q test and an I^2 higher than 75% indicate high heterogeneity between study outcomes (Higgins and Thompson, 2002).

Meta-regression analyses were conducted to examine the source of heterogeneity in research findings. Categorical moderators analyzed included Group (addiction or neurological disease), Task (flanker, go/no-go, or others), Medicine (on, off, or washout), ERN/Pe definition (response-locked or delta), Electrode (ERN: FCz, Fz, Cz, or others; Pe: Cz, CPz, Pz, or others). For the effect of Group, to get more detailed information about the difference, we reclassified it into two other moderators: Broad category (stimulants, depressants, acquired brain injury, basal ganglia disorders, white matter diseases, etc.) and Specific category (alcohol, tobacco, cannabis, cocaine, Parkinson, TBI, cerebellar lesion, prefrontal lesions, etc.). Three addiction-unique moderators (Severity: clinical vs. subclinical; Abstain status: yes vs. no; Treatment: yes vs. no) were examined within addiction-related studies only. Two continuous variables were transformed into categorical variables since they violated the assumption of normal distributions. They were Age (young: ≤39 yrs, middle-aged: 40–59 yrs, older: over 59 yrs) and the Percentage of males (majority are males vs. females). Since this is not individual-level meta-analyses, the mean age for each group (experimental and control) from all included papers were used. The function of Wald_test() from 'clubSandwich' was used to test differences across levels of moderators with small-sample corrections, which is similar to *F*-test but with denominator degrees of freedom that can take non-integer values (i.e., approximate Hotelling's T2 [AHT] *F* tests; Pustejovsky and Tipton, 2018). Because fewer than four effect sizes cause problems for small-sample corrected *F* tests in terms of power (Tanner-Smith et al., 2016; Tipton and Pustejovsky, 2015), we excluded all moderator levels with less than four effect sizes.

2.3.5. Small sample bias assessment

To examine the small sample effect (i.e., small studies can only be published with very high effect sizes), we first visualized the symmetry of the contour-enhanced funnel plot, then used a modified form of Egger's test (i.e., used RVE with CHE working model to account for effect size dependency) to examine the symmetry empirically (Atit et al., 2022).

3. Results

3.1. ERN amplitude

One influential case was detected (Beste et al., 2017), and the following analyses were performed without it. There were 103 (*k*) effect sizes from 46 (*m*) studies included. The overall mean weighted effect size was significant ($g = 0.471$, 95% CI [0.288, 0.655], $t(42.92) = 5.19$, $p < 0.001$), implying greater negativity in the experimental group compared to healthy controls across groups (see the forest plot in Fig. 2). Considerable heterogeneity was observed in the results obtained cross studies ($Q(102) = 332.01$, $p < 0.001$; $\tau^2 = 0.31$; $\sigma^2_b = 0.20$; $\sigma^2_w = 0.11$; $I^2_t = 72.52\%$; $I^2_b = 47.34\%$; $I^2_w = 25.18\%$).[2] A sensitivity analysis with a correlation level of within-stfudy outcomes set to the range 0–1 showed no differences in effect size or *SE*.

Beyond the overall significant mean effect size, our main concern was to examine the difference between addiction and neurological disease. We found a marginally significant difference between these two groups, $F(1, 34.7) = 3.97$, $p = 0.054$. The effect size was larger in the neurological disease group ($g = 0.61$, $t(26.93) = 4.63$, $p < 0.001$) than in the addiction group ($g = 0.27$, $t(15.27) = 2.53$, $p < 0.001$), though both were significant. The results for all moderating effects examined were summarized in Table 2. The effect of 'Specific category' was also significant, $F(6, 3.84) = 7.7$, $p = 0.04$, and the post-hoc tests revealed that the effect size of cocaine was larger than that of alcohol ($\beta = 0.64$, $p < 0.05$), TBI ($\beta = 0.64$, $p < 0.05$), and cerebellar lesion ($\beta = 0.76$, $p < 0.05$); the effect size of Parkinson disease was larger than that of alcohol ($\beta = 0.74$, $p < 0.001$), tobacco ($\beta = 0.60$, $p < 0.05$), TBI ($\beta = 0.76$, $p < 0.01$), and cerebellar lesion ($\beta = 0.87$, $p < 0.05$); and the effect size of prefrontal lesion was larger than that of alcohol ($\beta = 0.76$, $p < 0.05$) and TBI ($\beta = 0.78$, $p < 0.05$). However, these post-hoc test results were inconclusive since at least one party of the paired comparison was with less than 4 degrees of freedom, indicating that too few studies were available to allow firm conclusions.

Another significant moderator was Age ($F(2, 20.6) = 4.42$, $p < 0.05$). The effect size was significantly larger for older than for young adults ($\beta = 0.54$, $p < 0.01$), while the middle-aged group did not differ significantly from the other two groups (young adults: $\beta = -0.20$, $p = 0.30$; older: $\beta = 0.34$, $p = 0.15$). Other moderators examined did not significantly contribute to the heterogeneity of effect sizes, whereas certain levels of a moderator may differ from each other (see details in Table 2).

3.2. Pe amplitude

Three outliers were detected (Ito and Kitagawa, 2006, 2005; Solbakk et al., 2014), and the analyses included 47 effect sizes from 23 studies. The overall mean weighted effect size was not significant ($g = -0.14$, 95% CI [−0.297, 0.007], $t(18.15) = -2.00$, $p = 0.06$) (see the forest plot in Fig. 3). Moderate heterogeneity was observed in the results obtained

[2] Q = Cochrane's Q test for effect size heterogeneity; τ^2 = total variance; σ^2_b = variance between samples; σ^2_w = variance within samples; I^2_t = total amount of heterogeneity relative to the total amount of variance; I^2_b = amount of heterogeneity between samples relative to the total amount of variance; I^2_w = amount of heterogeneity within samples relative to the total amount of variance.

Table 1b
Characteristics of included studies (Neurological disease).

Study	Sample size (gender, age: mean±sd)	The sample size for ERN/Pe calculation	Education years (M ±SD)	Neurological disorder	Diagnostic criteria	Brain lesions	Task	Reference	Baseline/ms	Time window/ms	Nr of electrode	Electrodes analyzed
Beste et al. (2006)	11NDG(NA, 39.81 ± 8.96); 12CON(NA, 38.12 ± 7.56)	Same	NA	Huntington's disease	Genetic	Basal ganglia	Flanker	Linked mastoids	-200–0	ERN: NA; Pe: 200–500	32	ERN: Fz, Fcz, Cz; Pe: Pz
Beste et al. (2009)-a	15NDG (8 M,37.1 ± 7.4); 15 young CON (7 M,34.5 ± 5.5)	Same	comparable (mean years NA)	Huntington's disease	Genetic	Basal ganglia	Flanker	Linked mastoids	-200–0	ERN: NA	32	ERN: Fz, FCz, Cz
Beste et al. (2009)-b	17NDG off med (9 M,66.8 ± 8.5); 17 old CON(9 M,65.2 ± 7.2)	Same		Parkinson's disease	Clinical (Unified Parkinson's Disease Rating Scale)							
Beste et al. (2009)-c	17NDG de novo(7 M,59.6 ± 10.4); 17 old CON(9 M, 65.2 ± 7.2)	Same		Parkinson's disease	Clinical (Unified Parkinson's Disease Rating Scale)							
Beste et al. (2017)	21NDG(M, 47.6, SD=NA); 21CON(M, 47.1, SD=NA)	Same	NA	Parkinson's disease	Genetic (X-linked dystonia parkinsonism)	Basal ganglia	Flanker	Free/CSD	-800~ -600	ERN: 50–100	28	ERN: FCz, Cz
Falkenstein et al. (2001a)	15NDG (8 M,60.1, SD=NA); 15CON (8 M,60.2, SD=NA)	Task 1: 13NDG, 13CON; Task 2: 13NDG, 13CON; Task 3: 14NDG, 14CON	comparable (mean years NA)	Parkinson's disease	Clinical (Unified Parkinson's Disease Rating Scale)	Basal ganglia	Task 1: Flanker; Task 2: Simon; Task 3: GNG	Average	-200–0	ERN: -20–180	24	ERN: FCz
Falkenstein et al. (2005)	15NDG (8 M,60.1, SD=NA); 15CON (8 M,60.2, SD=NA)	Task 1: 13NDG, 13CON; Task 2: 13NDG, 13CON; Task 3: 14NDG, 14CON	comparable (mean years NA)	Parkinson's disease	Clinical (Unified Parkinson's Disease Rating Scale)	Basal ganglia	Task 1: Flanker; Task 2: Simon; Task 3: GNG	Average	-200–0	Pe: 250–550	24	Pe: Pz
Holroyd et al. (2002)	9NDG(M,56.1 ± 4.6); 9CON (M, 57.3 ± 5.9)	Same	NA	Parkinson's disease	Clinical (Unified Parkinson's Disease Rating Scale and the Hoehn and Yahr rating scale)	Basal ganglia	Flanker	Linked mastoids	NA	ERN: 0–200	20	ERN: Cz, Fz
Ito and Kitagawa (2006)	17NDG (8 M,64.1, SD=NA); 15CON (7 M,63.8, SD=NA)	Same	comparable (mean years NA)	Parkinson's disease	Clinical (Hoehn and Yahr rating scale)	Basal ganglia	Lexical decision task	Linked mastoids	-200–0	ERN: 10–200; Pe: NA	6	ERN: Fz; Pe: Pz
		Same				Basal ganglia	Flanker	Average	-200–0	ERN: NA	30	ERN: FCz

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Table 1b (*continued*)

Study	Sample size (gender, age: mean±sd)	The sample size for ERN/ Pe calculation	Education years (M ±SD)	Neurological disorder	Diagnostic criteria	Brain lesions	Task	Reference	Baseline/ ms	Time window/ ms	Nr of electrode	Electrodes analyzed
Seer et al. (2017)	13NDG (10 M,64.31 ± 8.6); 13CON (10 M, 63.15 ± 11.15)		NDG(13.04 ± 3.82); CON (13.65 ± 3.24)	Parkinson's disease	Clinical (experienced attending neurologists)							
Stemmer et al. (2007)-a	9NDG non-medicated (4 M,64.2, SD=NA); 14CON (5 M,65.6, SD=NA)	Same	NDG non-medicated (14.0, SD=NA); CON (14.5, SD=NA)	Parkinson's disease	Clinical (Unified Parkinson's Disease Rating Scale and the Hoehn and Yahr rating scale)	Basal ganglia	Flanker	Linked mastoids	-400∼ -200	ERN: 0–150	64	ERN: Fz, FCz, Cz, CPz, Pz
Stemmer et al. (2007)-b	9NDG medicated (6 M, 63.4, SD=NA); 14CON (5 M,65.6, SD=NA)	Same	NDG medicated (14.3, SD=NA); CON (14.5, SD=NA)	Parkinson's disease	Clinical (Unified Parkinson's Disease Rating Scale and the Hoehn and Yahr rating scale)	Basal ganglia	Flanker	Linked mastoids	-400∼ -200	ERN: 0–150	64	ERN: Fz, FCz, Cz, CPz, Pz
Verleger et al. (2013)	12NDG (9 M,65, SD=NA); 12CON (4 M,68, SD=NA)	9NDG; 9CON	NA	Parkinson's disease	Clinical (Unified Parkinson's Disease Rating Scale and the Hoehn and Yahr rating scale)	Basal ganglia	Flanker	Nose-tip	NA	ERN: 0–150	20	ERN: Fz, Cz, Pz
Volpato et al. (2016)	10NDG (7 M,56.3 ± 3.24); 10CON(4 M, 57.9 ± 7.5)	Same	NDG(12.0 ± 4.24); CON (13.1 ± 4.14)	Parkinson's disease	Clinical (United Kingdom PD Society brain bank diagnostic criteria)	Basal ganglia	Reinforcement learning task	Fpz	-800∼ -700	ERN: 0–150	29	ERN: Cz
Willemssen et al. (2008)	20NDG (12 M,64.5 ± 9.7); 20CON (12 M, 64.3 ± 8.9)	18NDG(66.3 ± 8.3); 18CON (66.0 ± 7.3)	comparable educational background (mean years NA)	Parkinson's disease	Clinical (Unified Parkinson's Disease Rating Scale)	Basal ganglia	Flanker	Average	NA	ERN: 20–120	26	ERN: FCz
Willemssen et al. (2009)	14NDG de novo(7 M,58.9 ± 10.4); 14CON(7 M, 59 ± 11.0)	Same	comparable (mean years NA)	Parkinson's disease	Clinical (experienced attending neurologists)	Basal ganglia	Flanker	Average	NA	ERN: 20–120	26	ERN: FCz
Ito and Kitagawa (2005)	16NDG (7 M,65.4, SD=NA); 15CON (7 M;63.8, SD=NA)	12NDG (6 M,61.1, SD=NA); 15CON (7 M,63.8, SD=NA)	comparable (mean years NA)	Alzheimer's disease	Clinical (NINCDS-ADRDA Alzheimer's Criteria)	Neurodegenerative disorders	Lexical recognition paradigm	Linked earlobes	-200–0	ERN: 10–150; Pe: NA	5	ERN: Fz; Pe: Cz
Mathalon et al. (2003)	12NDG (4 M,76.2 ± 5.7); 10CON (4 M, 75.3 ± 5.1)	Same	NDG(15.9 ± 1.8); CON (16.7 ± 1.6)	Alzheimer's disease	Clinical (NINCDS-ADRDA Alzheimer's criteria)	Neurodegenerative disorders	Picture-name verification task	NA	-50–0	Pe: 200–500	NA	ERN: Fz, Cz; Pe: Pz;
		Same					Flanker	Average		ERN: 0–130	256	

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Table 1b (*continued*)

Study	Sample size (gender, age: mean±sd)	The sample size for ERN/ Pe calculation	Education years (M ±SD)	Neurological disorder	Diagnostic criteria	Brain lesions	Task	Reference	Baseline/ ms	Time window/ ms	Nr of electrode	Electrodes analyzed
Thurm et al. (2013)	14NDG (5 M,70.6 ± 8.2); 16CON (7 M, 68.0 ± 3.4)		NDG(13.8 ± 2.3); CON (14.8 ± 2.7)	Mild Cognitive Impairment	Clinical (MCI criteria)	Neurodegenerative disorders			-200~ -100			ERN: Fz, FCz, Cz, PCz;
Olson et al. (2018)	25NDG (20 M,21.0 ± 2.3); 22CON (13 M, 20.5 ± 2.0)	25NDG; 20CON	NDG(14.0 ± 1.7); CON (13.8 ± 1.3)	TBI	Clinical (interview)	Diffused	Flanker	Linked mastoids	-400~ -200	ERN:0–100; Pe:200–400	64	ERN: Fz, FCz; Pe: Cz, Pz
Larson et al. (2009)	20NDG (16 M,30.9 ± 12.0); 20CON(9 M, 26.1 ± 9.9)	Same	NDG(13.3 ± 1.7); CON (14.2 ± 1.4)	TBI	Clinical (Glasgow Coma Scale) and structural (computerized tomography)	Diffused	Stroop task	Average	-200–0	ERN: 0–100; Pe: 200–400	64	EGI system positions, ERN: 4(FCz), 65(Cz), 5 and 55; Pe: 65(Cz), 18, 43, 30, 34(Pz)
Larson et al. (2012)	36NDG (18 M,21.6 ± 2.4); 46CON (22 M, 20.7 ± 2.2)	Same	NDG(14.3 ± 1.2); CON (14.1 ± 1.5)	TBI	Clinical (interview)	Diffused	Stroop task	Average	NA	ERN: 0–200; Pe: 200–400	128	EGI system positions, ERN: 7, 31, 55, 80, 106; Pe: 54, 55, 61, 62 [Pz], 78, 79
Pontifex et al. (2009)	30NDG (23 M,19.9 ± 1.2); 36CON (21 M, 19.4 ± 1.4)	Same	NDG(14.2 ± 1.1); CON (13.6 ± 1.4)	TBI	Clinical (American Academy of Neurology injury definition)	Diffused	Flanker	Linked mastoids	-100–0	ERN: 0–200; Pe: 200–500	64	ERN: FCz; Pe: Pz
Gehring and Knight (2000)	6NDG(4 M,69, SD=NA); 10 older CON (4 M,70, SD=NA)	Same	NA	Acquired brain injury	Structural (computerized tomography or magnetic resonance imaging)	PFC lesion	Letter-discrimination task	Linked mastoids	-100–0	ERN: 0–50;	19	ERN: Cz
Maier et al. (2015)-a	7NDG (7 M,54.7 ± 10.05); 7CON(7 M, 48.0 ± 8.81)	Same	NDG(11.0 ± 4.66); CON (13.7 ± 3.44)	Acquired brain injury	Structural (computerized tomography or magnetic resonance imaging)	PFC lesion	Flanker	Linked mastoids	-150~ -50	ERN: -10–90; Pe: 200–400	27	ERN: FCz; Pe: Pz
Maier et al. (2015)-b	7NDG(M,57.6 ± 13.33); 7CON(M, 48.0 ± 8.81)	Same	NDG(10.7 ± 5.37); CON (13.7 ± 3.44)	Acquired brain injury	Structural (computerized tomography or magnetic resonance imaging)	Brain damage lesion (non-frontal lesion)	Flanker	Linked mastoids	-150~ -50	ERN: -10–90; Pe: 200–400	27	ERN: FCz; Pe: Pz
Solbakk et al. (2014)	12NDG (6 M,48.0 ± 6.7); 14CON (9 M, 41.1 ± 12.4)	Same	NDG(13.1 ± 2.5); CON (13.1 ± 2.5)	Tumor or TBI	Structural (magnetic resonance imaging)	OFC lesion	Stop task	Average	-300–0	ERN: 60–140;	128	128 channel Geodesic Sensor Net, ERN: 7, 106, 31, 80;

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Table 1b (*continued*)

Study	Sample size (gender, age: mean±sd)	The sample size for ERN/Pe calculation	Education years (M ±SD)	Neurological disorder	Diagnostic criteria	Brain lesions	Task	Reference	Baseline/ms	Time window/ms	Nr of electrode	Electrodes analyzed
										Pe: 200–400		Pe: 7, 106, 31, 80
Ullsperger et al. (2002)-a	7NDG (6 M,50.7 ± 11.3), 9 older CON (4 M, 51.1 ± 8.5)	Same	NA	Acquired brain injury	Structural (magnetic resonance imaging)	Unilateral frontal lesion	Flanker	Linked mastoids	-100–0	ERN: NA; Pe: 300–450	29	ERN & Pe amplitude: overall(F3, Fz, F4, FC3, FCz, FC4, C3, Cz, C4, P3, Pz, P4)
Ullsperger et al. (2002)-b	6NDG (5 M,38.8 ± 9.5); 9 younger CON (7 M, 38.4 ± 8.9)	Same	NA	Acquired brain injury	Structural (magnetic resonance imaging)	Bilateral OFC lesion	Flanker	Linked mastoids	-100–0	ERN: NA; Pe: 300–450	29	ERN latency: FCz
Ullsperger and von Cramon (2006)-a	7NDG (5 M,54.6, SD=NA); 7CON (5 M,54.7, SD=NA)	Same	NDG(10.9, SD=NA); CON (11,SD=NA)	Acquired brain injury	Structural (magnetic resonance imaging)	PFC lesion	Flanker	Linked mastoids	NA	ERN: 0–120	28	ERN amplitude: overall(F3, FCz, F4, C3, Cz, C4, P3, Pz, P4); ERN latency: FCz
Ullsperger and von Cramon (2006)-b	9NDG (8 M,49.1, SD=NA); 9CON (8 M,49.8, SD=NA)	Same	NDG(11.3, SD=NA); CON (11.6, SD=NA)	Acquired brain injury	Structural (magnetic resonance imaging)	Basal ganglia	Flanker	Linked mastoids	NA	ERN: 0–120	28	ERN amplitude: overall(F3, FCz, F4, C3, Cz, C4, P3, Pz, P4); ERN latency: FCz
Hogan et al. (2006)	NDG(NA, 18, SD=NA); 11CON(NA, 17,SD=NA)	Same	NA	White matter diseases	Structural (magnetic resonance imaging)	White matter lesion	Choice-response task	Linked mastoids	-100–0	ERN: 0–200; Pe: 200–500	21	ERN: FCz; Pe: NA
López-Góngora et al. (2015)	27NDG (11 M,34.5 ± 7.5); 31CON (12 M, 37.5 ± 8.9)	Same	NDG(14.4 ± 2.8); CON (14.9 ± 3.0)	Multiple sclerosis	Clinical (modified McDonald's criteria)	White matter lesion	Stop task	Linked mastoids	-50–0	ERN: 0–100	19	ERN: Fz, Cz
Niessen et al. (2020)	24NDG(20 M, 56.4 ± 12.5); 32CON(20 M, 56.4 ± 10.1)	17NDG (13 M,53.6 ± 12.2); 24CON(15 M, 56.0 ± 9.4)	NA	Stroke	Structural (magnetic resonance imaging)	Left hemisphere	GNG	Free/CSD	-100–0	ERN: 0–150; Pe: 150–300	64	ERN: FCz; Pe: Cz
Peterburs et al. (2011)	6NDG (2 M,54.3 ± 12.5); 28CON(12 M, 47.0 ± 12.0)	Same	NA	Stroke	Structural (magnetic resonance imaging)	Thalamus	Antisaccade task	Linked mastoids	-100–0	ERN: 0–160;	30	ERN: FCz
Peterburs et al. (2012)	8NDG (4 M,42.9 ± 8.9); 22CON	Same	NA	Stroke	Structural (magnetic	Cerebellum	Antisaccade task	Linked mastoids	-100–0 or -200~ -100	ERN: 0–160;	30	ERN: FCz; Pe: CPz

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Table 1b (*continued*)

Study	Sample size (gender, age: mean±sd)	The sample size for ERN/Pe calculation	Education years (M ±SD)	Neurological disorder	Diagnostic criteria	Brain lesions	Task	Reference	Baseline/ms	Time window/ms	Nr of electrode	Electrodes analyzed
	(11 M, 43.1 ± 2.1)				resonance imaging)					Pe: 150–450		
Peterburs et al. (2015)	16NDG (9 M,56.3 ± 9.7); 16CON (7 M, 56.1 ± 8.2)	16NDG; 15CON	NA	Acquired brain injury	Clinical (experienced attending neurologist)	Brain lesions (cerebellar lesions)	Antisaccade task	Linked mastoids	-200∼-100	ERN: 0–120; Pe: 200–400	28	ERN: Fz; Pe: Pz
Seifert et al. (2011)	15NDG (10 M;44.7 ± 13.07); 15CON(10 M; 44.4, SD=NA)	Same	NDG(10.8, SD=NA); CON (10.9, SD=NA)	Acquired brain injury	Structural (magnetic resonance imaging)	Thalamus	Flanker	Linked mastoids	NA	ERN: 0–140; Pe: 300–500	64	ERN & Pe: F3, FCz, F4, C3, Cz, C4, P3, Pz, P4

Note. NA: not available; Gender: M: all are males, F: all are females, X: mixed (the specific number for males and females was coded if it was reported, e.g., 17 M); NDG: neurological disorder group. CON: control group; GNG: go/no-go task; TBI: Traumatic brain injury

cross studies ($Q(46) = 99.24$, $p < 0.001$; $\tau^2 = 0.07$; $\sigma_b^2 < 0.01$; $\sigma_w^2 = 0.07$; $I_t^2 = 42.46\%$; $I_b^2 < 0.01\%$; $I_w^2 = 42.46\%$). This indicated that the heterogeneity mainly derived from within-study variance. Therefore, we only analyzed the three moderators (i.e., Electrode, Task, and Pe definition) with levels varied within studies and the effect of Group as of our interest. It revealed that, most importantly, the effect of Group was not significant ($F(1, 18.1) = 0.003$, $p = 0.96$), indicating that effect sizes were negligible in both addiction and neurological disease groups; nor were the effects of Electrode ($F(3, 8.62) = 0.604$, $p = 0.63$), Task ($F(2, 7.44) = 1.31$, $p = 0.33$), and Pe definition ($F(1, 5.76) = 0.19$, $p = 0.68$, Table 3).

3.3. ERN latency

Two outliers were detected (Ito and Kitagawa, 2005; Larson et al., 2012), and the analyses were performed with the remaining 37 effect sizes from 19 studies. The overall mean weighted effect size was not significant ($g = -0.13$, 95% CI [−0.297, 0.04], $t(15.26) = -1.63$, $p = 0.12$) (see the forest plot in Fig. 4). Small heterogeneity was observed in the results obtained cross studies ($Q(36) = 49.36$, $p = 0.07$; $\tau^2 = 0.03$; $\sigma_b^2 < 0.01$; $\sigma_w^2 = 0.03$; $I_t^2 = 19.34\%$; $I_b^2 < 0.01\%$; $I_w^2 = 19.34\%$). Therefore, we only analyzed the effect of Group as of our interest. It showed that the effect size of the neurological disease group ($g = -0.30$, $t(8.37) = -3.95$, $p < 0.01$) was more negative than that of the addiction group ($g = -0.01$, $t(6.96) = -0.10$, $p = 0.93$, $F(1, 15.2) = 4.96$, $p = 0.04$).

3.4. Pe latency

One outlier was detected (Ito and Kitagawa, 2005), and the analyses were performed with the remaining 20 effect sizes from 10 studies. The overall mean weighted effect size was not significant ($g = -0.16$, 95% CI [−0.372, 0.057], $t(7.37) = -1.72$, $p = 0.13$) (see the forest plot in Fig. 5). Small heterogeneity was observed in the results obtained cross studies ($Q(19) = 27.73$, $p = 0.09$; $\tau^2 = 0.01$; $\sigma_b^2 < 0.01$; $\sigma_w^2 = 0.01$; $I_t^2 = 9.95\%$; $I_b^2 < 0.01\%$; $I_w^2 = 9.95\%$). Therefore, we only analyzed the effect of Group, and it was not significant ($F(1, 6.85) = 0.179$, $p = 0.69$), indicating that effect sizes were negligible in both addiction and neurological disease groups.

3.5. Small sample bias assessment

For ERN amplitude, there was a significant relationship between effect size estimate and precision, $\beta = 2.92$, $SE = 0.77$, $t(18.9) = 3.78$, $p < 0.01$, indicating possible small sample bias (see funnel plot in Fig. 6). However, the Egger's test for neurological disease ($\beta = 2.78$, $SE = 1.47$, $t(9.8) = 1.90$, $p = 0.09$) and addiction ($\beta = 1.99$, $SE = 1.41$, $t(6.14) = 1.41$, $p = 0.21$) separately did not show publication bias. For Pe amplitude ($\beta = -1.38$, $SE = 1.12$, $t(9.94) = -1.23$, $p = 0.25$), ERN latency ($\beta = -0.28$, $SE = 1.19$, $t(7.93) = -0.24$, $p = 0.83$), and Pe latency ($\beta = 1.16$, $SE = 2.12$, $t(3.50) = 0.55$, $p = 0.62$), the Egger's test were not significant and their funnel plots did not indicate severe asymmetry (Fig. S1-S3), which implied no small sample bias.

3.6. Quality assessment

The 49 included studies were of moderate to high quality, with a mean score of 83.98% (68.75% ∼100%), according to the AXIS (Table 4). The main limitations were the small sample size and the unclear methods used to determine the sample size. For a few studies, information about participants' recruitment channels, descriptive statistics, and limitations was missing.

4. Discussion

The present meta-analysis examined whether addiction and

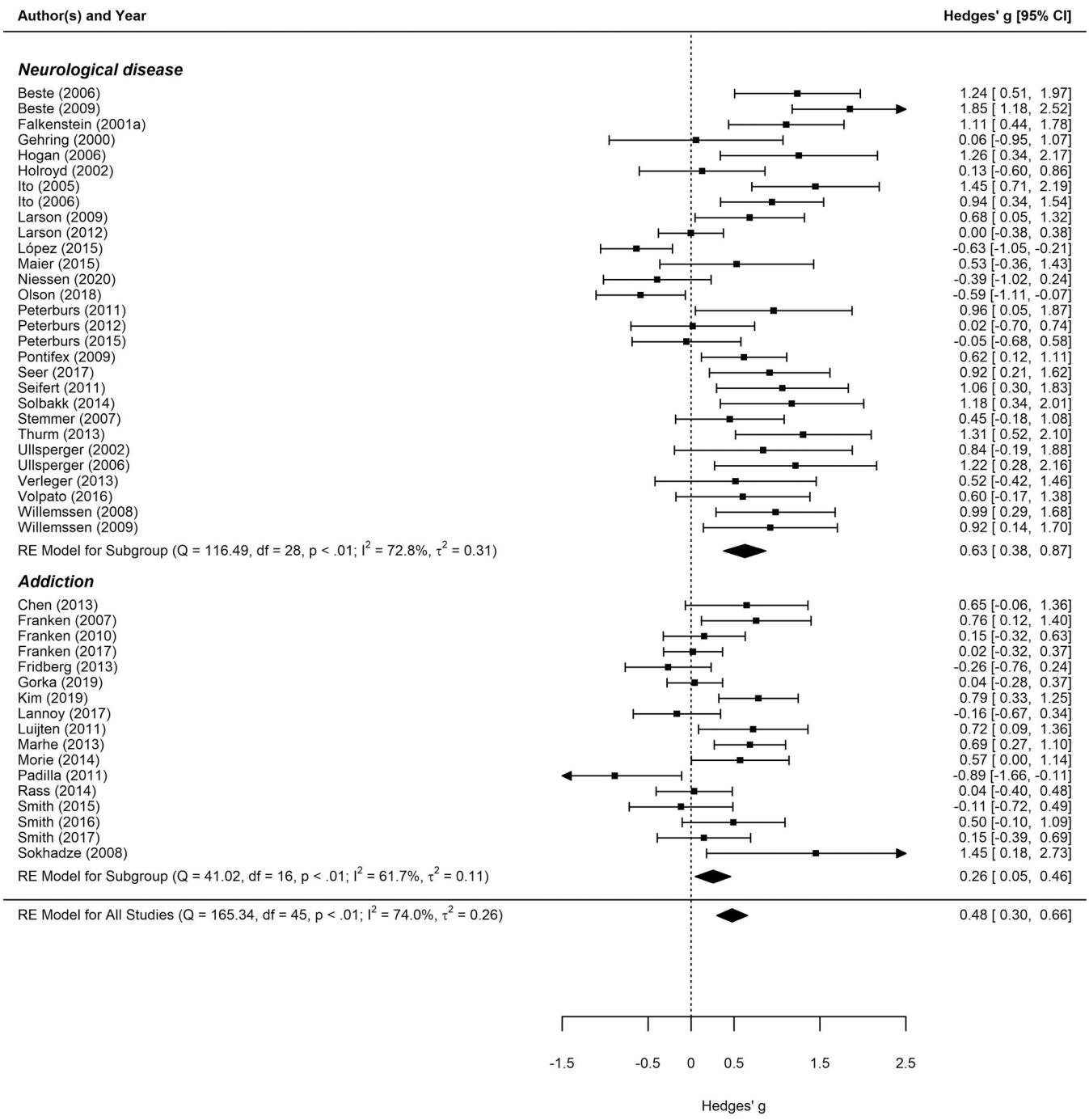

Fig. 2. Forest plot of ERN amplitude. The pooled effect size in this figure was calculated by making use of aggregated effect sizes per study, and therefore differs from the values reported in the main text when effect size dependency was controlled by RVE-CHE. This also applies to the other three forest plots.

neurological disorders were associated with compromised error processing (reflected by ERN amplitude, ERN latency, Pe amplitude, and Pe latency). Given the considerable degrees of heterogeneity, the effect of Age, Task, Medicine, Electrode, ERN/Pe definition, and Percentage of males were examined. We found that: 1) both addiction and neurological disorders were associated with compromised ERN amplitude, and the impairment was marginally larger in the latter sample; 2) Age was a significant moderator of ERN amplitude, with older adults showing more severe impairment than young adults; 3) neurological disorders presented shorter ERN latencies than addiction when compared with controls; 4) for Pe amplitude and Pe latency, all examined moderators including Group were not significant. In the following sections, we start discussing the main findings and the explanation, followed by implications, limitations, and suggestions for future studies.

4.1. Summary of results

Out of the four examined ERP indexes, ERN amplitude represented the most robust evidence and the richest results. We found that a decrement accompanied both addiction and neurological disorders in ERN amplitude, and such impairment was considerably larger in neurological disorders, although the group difference attained only marginal significance. The results for addiction were in line with some previous meta-analyses (Lutz et al., 2021; Pasion and Barbosa, 2019) but

Table 2
Moderator analysis of the overall effect size of ERN amplitude.

Moderator	*m*	*k*	*F*	*g*	*SE*	*t*	*df*	*p*	CI low	CI high
Group	46	103	F(1, 34.7) = 3.97					0.054		
Addiction	17	40		0.271	0.107	2.532	15.27	0.023	0.043	0.500
Neurological disease	29	63		0.610	0.132	4.629	26.93	0.000	0.339	0.880
Specific category	36	83	F(6, 3.82) = 7.76					0.037		
Alcohol	8	20		0.110	0.140	0.785	6.19	0.461	-0.230	0.449
Cocaine	4	8		0.746	0.083	8.964	2.31	0.008	0.430	1.062
Tobacco	3	10		0.249	0.179	1.387	1.91	0.305	-0.558	1.055
Parkinson	11	30		0.853	0.134	6.364	9.39	0.000	0.551	1.154
TBI	4	6		0.092	0.273	0.336	2.77	0.761	-0.820	1.003
Cerebellar lesions	2	4		-0.018	0.036	-0.503	1.00	0.703	-0.478	0.442
Prefrontal lesions	4	5		0.867	0.305	2.846	2.97	0.066	-0.108	1.842
Broad category	43	99	F(4, 5.31) = 2.38					0.177		
Acquired brain injury	14	22		0.344	0.165	2.091	12.04	0.058	-0.014	0.703
Basal Ganglia Disorders	11	33		0.891	0.147	6.052	9.70	0.000	0.561	1.220
Depressants	9	21		0.136	0.140	0.971	7.47	0.362	-0.191	0.464
Stimulants	7	18		0.516	0.146	3.543	5.41	0.014	0.150	0.883
White matter diseases	2	5		-0.076	0.861	-0.088	1.00	0.944	-11.020	10.868
Age	46	103	F(2, 20.6) = 4.42					0.025		
Young	21	49		0.299	0.130	2.299	19.25	0.033	0.027	0.570
Middle-aged	16	28		0.495	0.147	3.356	14.05	0.005	0.179	0.811
Old	10	26		0.837	0.117	7.148	8.39	0.000	0.569	1.104
Task	46	103	F(2, 7.8) = 0.522					0.612		
Flanker	27	66		0.517	0.112	4.609	25.34	0.000	0.286	0.748
GNG	6	9		0.310	0.175	1.768	4.13	0.150	-0.171	0.790
Others	16	28		0.441	0.162	2.719	14.37	0.016	0.094	0.789
Medicine	22	56	F(2, 2.48) = 0.102					0.907		
On	7	15		0.572	0.197	2.899	6.54	0.025	0.099	1.045
Off	14	33		0.637	0.173	3.676	15.30	0.002	0.268	1.006
Overnight washout	5	8		0.532	0.170	3.135	4.95	0.026	0.095	0.970
ERN definition	46	103	F(1, 11.2) = 1.51					0.244		
Delta	13	20		0.673	0.180	3.744	12.98	0.002	0.285	1.061
Response locked	39	83		0.421	0.108	3.885	39.14	0.000	0.202	0.640
Electrode	46	103	F(3, 12.1) = 0.295					0.829		
Cz	15	21		0.458	0.128	3.586	17.02	0.002	0.189	0.728
FCz	23	35		0.481	0.116	4.145	24.00	0.000	0.241	0.720
Fz	15	21		0.379	0.127	2.975	17.71	0.008	0.111	0.647
Others	17	26		0.524	0.178	2.935	14.91	0.010	0.143	0.904
Percentage male	44	99	F(1, 17.3) = 0.0128					0.911		
Female major	28	49		0.430	0.146	2.951	18.46	0.008	0.124	0.735
Male major	20	50		0.449	0.107	4.191	26.08	0.000	0.229	0.670
Addiction: severity	17	40	F(1, 6.5) = 2.57					0.156		
Clinical	9	14		0.414	0.151	2.752	7.24	0.028	0.061	0.768
Subclinical	10	26		0.162	0.111	1.462	9.08	0.178	-0.088	0.412
Addiction: abstain	17	40	F(1, 4.72) = 0.159					0.707		
No	13	31		0.239	0.098	2.450	10.97	0.032	0.024	0.454
Yes	5	9		0.335	0.240	1.395	3.61	0.243	-0.361	1.030

Note. F: AHT F test; *p*: p-value of AHT-F test for moderator effect or t-tests that compare each level against zero

not all (Zhang et al., 2021). For instance, Lutz et al. (2021) found an overall significant effect for external behaviors, including addiction, and the diagnosis was not a moderator. Pasion and Barbosa (2019) reported that the effect size was not significant for alcohol-related studies, similar to what we found. Zhang et al. (2021) highlighted how the effect size was significant only when small sample-sized studies were excluded ($N < 20$ in each group), whereas we found it significant irrespective of sample size. This inconsistency may be due to different inclusion and exclusion criteria applied (e.g., only use data from Cz or Fz electrodes in Zhang et al., 2021 vs. making use of as much data as possible in ours) and different analytic approaches used to address the effect size dependency. Furthermore, we found that stimulants in general and cocaine in specific were associated with more severe impairments in ERN amplitude, which resembled the results of a meta-analysis on motor inhibition (Smith et al., 2014). These findings stressed the effect of stimulant use, with cocaine in particular, on dopaminergic and serotonergic prefrontal-subcortical pathways that are critical for cognitive control. As to interpreting the cross-group similarities, we may speculate that addiction as well as dopamine-related neurological disorders such as Parkinson's disease are characterized by a significant loss of dopaminergic neurons in the substantia nigra and of their projections into the striatum and prefrontal cortex, whose dopamine levels play an important role in the generation of the ERN (Gramage and Herradon, 2011; Jocham and Ullsperger, 2009).

Furthermore, Age was found as an important moderator of ERN amplitude, such that the effect size for the older group (over 59 yrs) was larger than that of the young adult group (≤39 yrs), implying more serious error processing deficits. This is in line with Boen et al. (2022), who showed that ERN amplitude peaks in young adults. One potential reason is that normal aging is accompanied by gradual degradation of the mesocorticolimbic dopaminergic system, which plays an important role in error processing (Beste et al., 2009; Falkenstein et al., 2001b; Nieuwenhuis et al., 2002; Ridderinkhof and Krugers, 2022). The absence of an age effect in two other relevant meta-analyses (Lutz et al., 2021; Vallet et al., 2021) likely pertains to the absence of a group of older adults since they did not include neurological disorders-related studies.

In addition, we did not find a moderating effect of Medicine, which was in line with previous studies that showed neither an acute nor a chronic medicine effect (Stemmer et al., 2007; Willemssen et al., 2008), implying that the reduction of ERN was unaffected by medicine status. We also did not find the Task used to elicit errors to be a significant moderator. This seemingly conflicts with Lutz et al. (2021); however, ERN amplitude has been shown to be highly correlated across different tasks (Riesel et al., 2013; Segalowitz et al., 2010). We also did not find

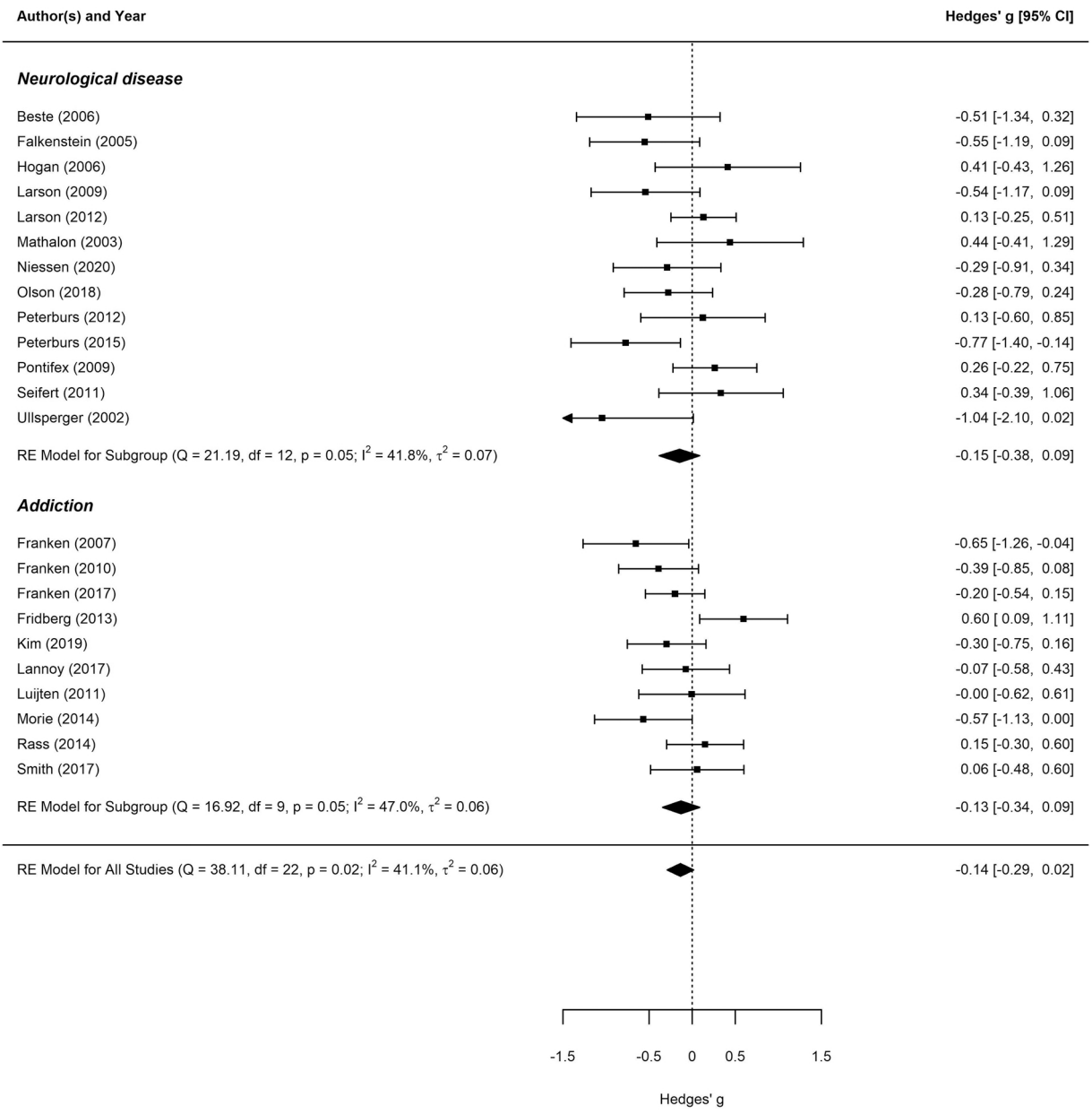

Fig. 3. Forest plot of Pe amplitude.

Table 3
Moderator analysis of the overall effect size of Pe amplitude.

Moderator	*m*	*k*	*F*	*g*	*SE*	*t*	*df*	*p*	CI low	CI high
Group	23	47	F(1, 18.1) = 0.003					0.958		
Addiction	10	28		-0.142	0.094	-1.505	8.12	0.170	-0.358	0.075
Neurological disease	13	19		-0.150	0.119	-1.262	10.04	0.236	-0.414	0.115
Electrode	23	47	F(3, 8.62) = 0.604					0.629		
CPz	6	8		-0.019	0.154	-0.124	4.89	0.906	-0.419	0.381
Cz	8	11		-0.162	0.117	-1.384	6.51	0.212	-0.442	0.119
Pz	8	11		-0.291	0.131	-2.223	6.97	0.062	-0.600	0.019
Others	12	17		-0.120	0.096	-1.250	9.63	0.241	-0.335	0.095
Task	23	47	F(2, 7.44) = 1.31					0.326		
Flanker	12	26		-0.210	0.072	-2.917	8.99	0.017	-0.372	-0.047
GNG	5	8		-0.276	0.186	-1.487	3.65	0.218	-0.813	0.260
Others	9	13		0.038	0.140	0.271	6.78	0.795	-0.296	0.372
Pe definition	23	47	F(1, 5.76) = 0.188					0.680		
Delta	6	7		-0.073	0.185	-0.391	4.94	0.712	-0.551	0.406
Response locked	22	40		-0.159	0.078	-2.039	17.11	0.057	-0.324	0.005

Note. F: AHT F test; *p*: p-value of AHT-F test for moderator effect or t-tests that compare each level against zero

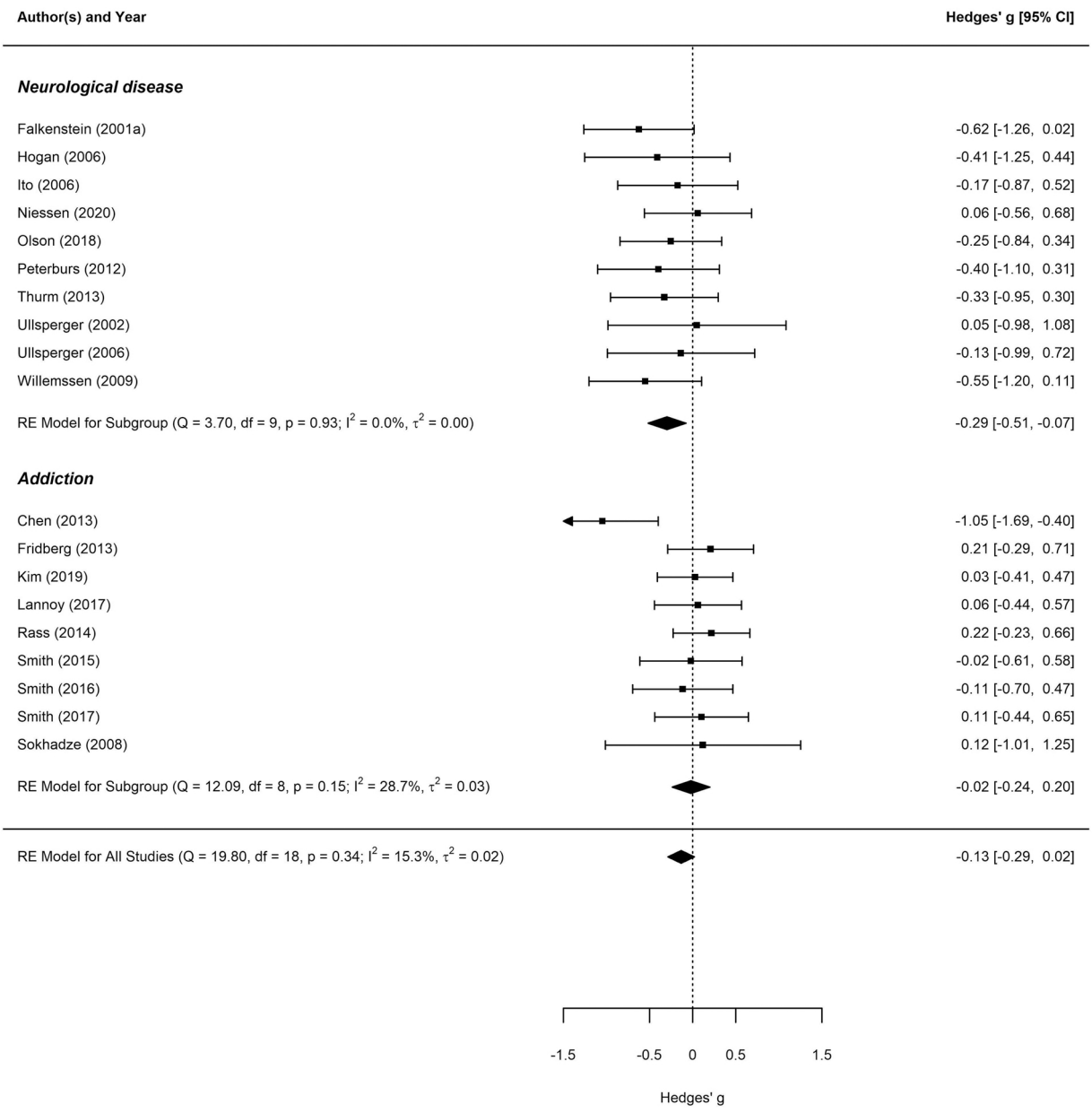

Fig. 4. Forest plot of ERN latency.

the Task used to elicit errors to be a significant moderator, which was in line with Lutz et al. (2021). Furthermore, ERN amplitude has been shown to be highly correlated across different tasks (Riesel et al., 2013; Segalowitz et al., 2010). Though Pasion and Barbosa (2019) found a larger effect size when go/no-go rather than other tasks were used, an evaluation of the moderating effect of Task is lacking. In exploratory analyses, we did not find that Electrode, Percentage of males, or ERN definition (delta/response-locked) contributed significantly to the effect size heterogeneity, nor did Severity (clinical/subclinical) and Abstinence status within addiction-related studies.

For ERN latency, the effect size for neurological disorders was more negative than that of addiction, indicating faster error processing speed. This result seems counterintuitive since the impaired error-processing ability is expected to be accompanied by delayed error-processing speed. One might speculate that impairment in error-processing circuitry is associated with a 'quick-and-dirty' trajectory of error detection, leading to premature false negatives that could have been prevented by more deliberate error processing. Of note, though ERN latency alteration was significant in neurological disorders, only one included study reported significantly shorter latency in Parkinson's disease patients than in healthy controls, which was explained as a reflection of reduced ERN amplitude instead (Falkenstein et al., 2001a).

Several others indicated numerical differences between patients and controls (Hogan et al., 2006; Olson et al., 2018; Peterburs et al., 2012; Thurm et al., 2013). For addiction-related studies, most effect sizes approached zero, suggesting no apparent difference from the control group. In sum, the effect of Group should be explained with caution and more studies were needed to validate the present finding.

For Pe amplitude, none of the examined within-study moderators showed significant effects. The negative result of Task conflicts with that reported by Lutz et al. (2021), where the go/no-go task was found to induce larger group differences than the flanker task. Although a significant effect size was found here for the flanker task, it did not differ significantly from the ones when other tasks were used, resulting in a non-significant moderating effect of Task. Reasons similar to those used to explain the discrepant findings about ERN amplitude may also apply here. As exploratory moderators, Electrode and Pe definition (delta/response-locked) were not found to contribute significantly to the effect

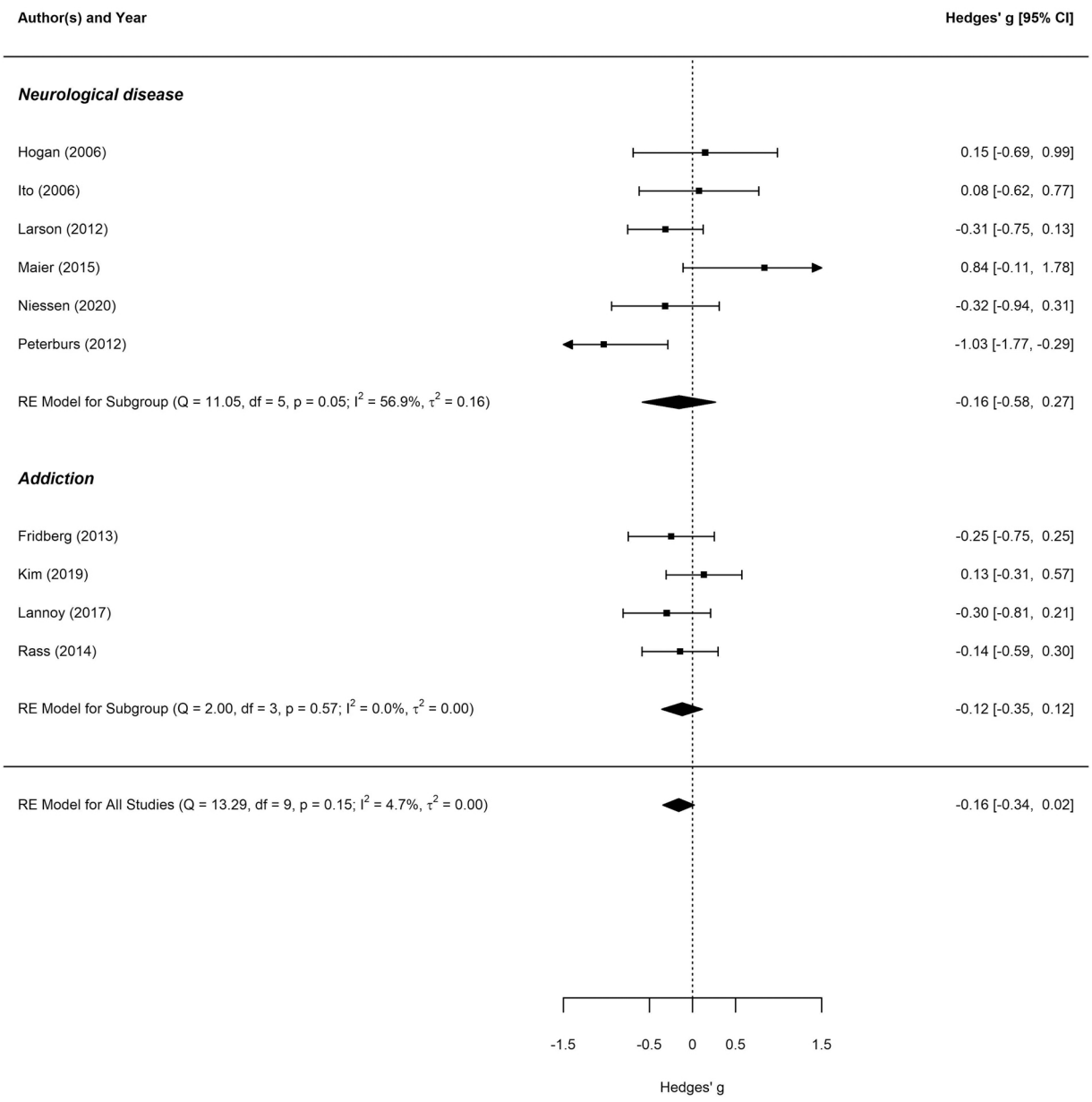

Fig. 5. Forest plot of Pe latency.

size heterogeneity. Furthermore, no Group effect was found for both Pe amplitude and Pe latency, implying impairments in later stages of error processing that were comparable between addiction and neurological disorders.

4.2. Implications

A central feature of addictive behavior is the person's apparent lack of voluntary control over drug self-administration, despite their awareness of the severe adverse consequences of continued use. According to the process model of self-control failure, a deficient monitoring network leads to insufficient mobilization of the cognitive control network, which results in self-control failure by increasing the value of short-term over long-term outcomes when computing the integrated value of an action (Goschke, 2014; Inzlicht et al., 2015; Kotabe and Hofmann, 2015). Similarly, Luijten et al. (2014) postulated that error processing deficits might indirectly influence other cognitive control domains, including inhibitory control. This fundamental role of error processing in self-control was the main impetus for our present focus on this research topic. Furthermore, several prospective studies suggested that ERN and Pe indices may serve as biomarkers of behavioral changes in treatment for substance use disorder (e.g., treatment discontinuance: Steele et al., 2014; relapse: Luijten et al., 2016; Marhe et al., 2013), indicating their clinical relevance. We do not mean to neglect the role of other core constructs in the development of addiction, as defined by a recent Delphi study (Yücel et al., 2018). However, compared to error-processing impairments, these other components were relatively less studied in neurological disorders, thus hampering intergroup comparison.

In line with the brain disease model of addiction, a previous review reported that people with long-term abuse showed neuropsychological impairments of executive (inhibitory) control, working memory, and decision-making, together with neurobiological alterations in the frontotemporal and basal ganglia circuits (Yücel et al., 2007). Also a recent meta-analysis found alterations in gray matter and white matter in substance use disorders depending on the severity of the consumption pattern and type of substance used (Pando-Naude et al., 2021). The present study is the first attempt to examine the degree of brain disorder

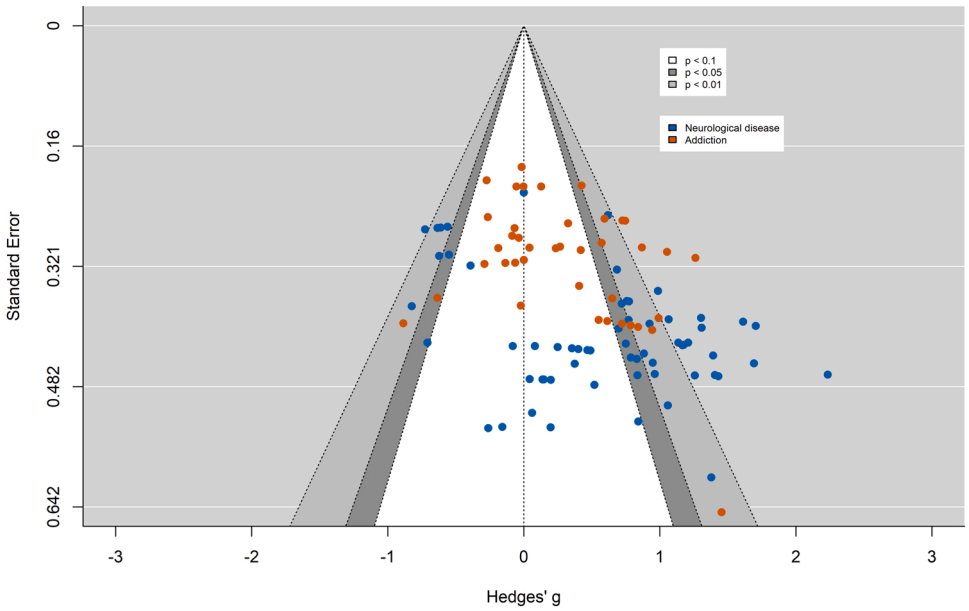

Fig. 6. Funnel plot of ERN amplitude.

of addiction by contrasting it with a sample of well-defined brain disorders. We approached this aim by using available data and applying recently developed methods to address effect size dependency (Pustejovsky and Tipton, 2022). Our analyses confirm that addiction is associated with brain functional changes, expressed in significantly diminished ERN amplitude. While it remains difficult to establish beyond doubt whether the changes in ERN are caused by drug abuse or are predisposing factors, it may be noted that some endophenotype research indicated that diminished ERN (as observed in unaffected relatives) holds potential as a risk factor for substance use disorders (Euser et al., 2013; Riesel et al., 2019). For instance, Euser et al., (2013) showed that ERN was already reduced before substance use onset in the offspring of substance use disorder parents. Alterations in ERN amplitude in unaffected first-degree relatives with a family history of substance abuse disorder support the utility of the ERN as a transdiagnostic endophenotype. Reduced ERNs may indicate vulnerability for under-controlled behavior and risk for substance (ab)use. The finding that this impairment was not (or only marginally) moderated by Group offers novel support for the suggestion that addiction can be considered a brain disorder, similar to other neurological diseases.

Nonetheless, considering the pattern of findings for the ERN (less compromised amplitude and delayed latencies for addiction than neurological disorders, although the former effect just failed to attain statistical significance), the observed error-processing deficiency in addiction does not allow us to simply equate addiction with conventional brain pathologies such as various neurological disorders in terms of the brain dysfunction level. Therefore, rather than struggling over a label, the crux of the matter is to quantify the degree of dysfunctions in addiction and examine whether these dysfunctions preclude individuals' capacity to alter their behavior based on foreseeable consequences like typical brain disorders do (Satel and Lilienfeld, 2014). A bold suggestion is that instead of perceiving addiction and neurological disorders as identical or distinct patterns, they may represent nuances within a spectrum of brain pathology, which comes to expression in error processing.

Of note, the neurocentric view of addiction does not downplay the influence of social, environmental, developmental, or socioeconomic processes as both causes and consequences of substance use, but instead assumes the brain as the underlying material substrate upon which those factors come to play and from which the responses originate (Heilig et al., 2021).

4.3. Limitations and future study suggestions

A couple of limitations should be acknowledged. First, all studies included were required to have an experimental group and a control group, which made assessing the continua of the full range of symptoms impossible. For addiction, we coded clinical and subclinical samples to tap this continuum, and it turned out that this factor did not moderate error processing. By contrast, it is hard to quantify the severity of neurological disorders across complaints consistently. For instance, cognitive deterioration develops over time in progressive neurodegenerative disorders (e.g., Alzheimer's disease and Parkinson's disease; Gao and Hong, 2008), which is not necessarily the case for traumatic brain injury. Second, we excluded studies having participants with comorbid disorders (e.g., anxiety, ADHD) to eliminate the confounding effect. For instance, alcohol use disorder is often combined with anxiety disorder which is associated with enhanced ERN amplitude (Schellekens et al., 2010). Albeit relatively pure substance and neurological disease effect were obtained, this practice hampered the generalization of conclusions since these two samples are likely to have comorbidities that bias error processing (Pasion and Barbosa, 2019; Seow et al., 2020). Future studies are recommended to record and report comorbid disorders consistently, which allows isolating relevant effects neatly through statistical analysis rather than paper removal. Third, unlike addiction, most neurological diseases need medical treatment. However, detailed medical use history was often unavailable, which if accessible would likely outperform the coarse measure of on/off/overnight washout in evaluating the medical effect. Given the concerns of the last two points, studies in the future are encouraged to increase transparent reports of moderators that may help explain heterogeneity in the results. Fourth, we did not include behavioral addiction since too little published evidence is available to allow running a separate meta-analysis. However, we can imagine that along with the forthcoming accumulation of evidence, the pharmacological effects of substances on error processing can be isolated from non-pharmacological factors through meta-regression analysis. Fifth, we did not explicitly require all included studies to have at least six error trials for a reliable ERN estimation (Olvet and Hajcak, 2009), but assumed that authors complied with this rule of thumb by default. More strictly speaking, a recent meta-analysis indicated that 16 error trials were needed for internal consistency of 0.80 (Clayson, 2020). Studies in the future may examine the effect number of error trials by treating it as a moderator. Still, seven influential effect sizes were excluded from the

Table 4
Quality assessment of studies included according to the AXIS.

Ref	Q1/ aim clear?	Q2/ design proper for aim?	Q3/ sample size justified?	Q4/target population clear?	Q5/ sample frame proper?	Q6/ participants selected properly?	Q7/IV and DV measurement validity	Q8/IV and DV measurement reliability	Q9/ significance and precision (p and /or CI)	Q10/can methods be replicated?	Q11/basic data described adequately?	Q12/results internally consistent?	Q13/ present the results for all analysis in methods?	Q14/ discussion and conclusion justified by results?	Q15/ limitation discussed?	Q16/ ethics and consent form	% score
Beste et al. (2006)	Y	Y	N	Y	Y	Y	Y	Y	y	Y	N	Y	Y	Y	N	Y	81.25
Beste et al. (2009)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	81.25
Beste et al. (2017)	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N	Y	75
Falkenstein et al. (2001a)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	75
Falkenstein et al. (2005)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N	75
Gehring and Knight (2000)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	75
Hogan et al. (2006)	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	81.25
Holroyd et al. (2002)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	81.25
Ito and Kitagawa (2005)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	75
Ito and Kitagawa (2006)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	N	75
Larson et al. (2009)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	93.75
Larson et al. (2012)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	87.5
López et al. (2015)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	93.75
Maier et al. (2015)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	93.75
Mathalon et al. (2003)	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N	N	68.75
Niessen et al. (2020)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	87.5
Olson et al. (2018)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	y	Y	Y	Y	Y	Y	93.75
Peterburs et al. (2011)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	81.25
Peterburs et al. (2012)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	87.5
	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	81.25

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Table 4 (*continued*)

Ref	Q1/ aim clear?	Q2/ design proper for aim?	Q3/ sample size justified?	Q4/target population clear?	Q5/ sample frame proper?	Q6/ participants selected properly?	Q7/IV and DV measurement validity	Q8/IV and DV measurement reliability	Q9/ significance and precision (p and /or CI)	Q10/can methods be replicated?	Q11/basic data described adequately?	Q12/results internally consistent?	Q13/ present the results for all analysis in methods?	Q14/ discussion and conclusion justified by results?	Q15/ limitation discussed?	Q16/ ethics and consent form	% score
Peterburs et al. (2015)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	87.5
Pontifex et al. (2009)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	87.5
Seer et al. (2017)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	87.5
Seifert et al. (2011)	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	81.25
Solbakk et al. (2014)	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	N	Y	75
Stemmer et al. (2007)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	81.25
Thurm et al. (2013)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	81.25
Ullsperger et al. (2002)	Y	Y	N	Y	Y	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y	75
Ullsperger and von Cramon (2006)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	81.25
Verleger et al. (2013)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	81.25
Volpato et al. (2016)	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	87.5
Willemssen et al. (2008)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	81.25
Willemssen et al. (2009)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	N	Y	75
Chen et al. (2013)	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	81.25
Franken et al. (2007)	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	81.25
Franken et al. (2010)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	81.25
Franken et al. (2017)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	87.5
	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	93.75

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Table 4 (*continued*)

Ref	Q1/ aim clear?	Q2/ design proper for aim?	Q3/ sample size justified?	Q4/target population clear?	Q5/ sample frame proper?	Q6/ participants selected properly?	Q7/IV and DV measurement validity	Q8/IV and DV measurement reliability	Q9/ significance and precision (p and /or CI)	Q10/can methods be replicated?	Q11/basic data described adequately?	Q12/results internally consistent?	Q13/ present the results for all analysis in methods?	Q14/ discussion and conclusion justified by results?	Q15/ limitation discussed?	Q16/ ethics and consent form	% score
Fridberg et al. (2013)	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	93.75
Gorka et al. (2019)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
Kim and Kim (2019)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	87.5
Lannoy et al. (2017)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	87.5
Luijten et al. (2011)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	93.75
Marhe et al. (2013)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	87.5
Morie et al. (2014)	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	75
Padilla et al. (2011)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	93.75
Rass et al. (2014)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	87.5
Smith et al. (2015)	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	93.75
Smith et al. (2016)	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	87.5
Smith et al. (2017)	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y	N	Y	68.75
Sokhadze et al. (2008)																	

Note. N = No; Y = Yes; IV: independent variable; DV: dependent variable; CI: confidence interval

analyses, potentially due to uncommon tasks used (e.g., lexical recognition paradigm: Ito and Kitagawa, 2005) and broad sources of ERN and Pe activities when 128 channel caps were used (e.g., Larson et al., 2012; Solbakk et al., 2014). Studies in the future may want to take these methodological considerations into account. Furthermore, while our understanding of differences in ERN and Pe latencies remains limited at present, and the focus in the empirical literature has been on amplitude, nonetheless some studies have examined (and reported effects on) latency, and we cannot exclude that such effects are meaningful and might be corroborated by meta-analysis. For instance, several studies have drawn analogies between the Pe and P3, both in terms of functional significance and underlying sources (e.g., Ridderinkhof et al., 2009). P3 latency has often been found to be meaningfully affected by experimental effects and group or individual differences. For example, No-go P3 latency has been argued to reflect the slowing of inhibition processing (as explored further in a meta-analysis by Cheng et al., 2019). Interpreting delayed latency as impaired cognitive processing speed might not be limited to inhibition, and can potentially be expanded to error processing. Concerning ERN latency, some studies have suggested that delayed ERN latency may be interpreted as a delay in upregulating cognitive control processes following an error (e.g., Larson et al., 2012). Since meta-analytic outcomes might help in generating hypotheses (or, instead, confirm that latency is not fruitful as a measure to include in further studies), we included explorative analyses of latencies in the present meta-analysis.

5. Conclusions

The current meta-analyses compared 17 addiction-related and 32 neurological disorder-related studies regarding electrophysiological indexes of error processing. The main finding is that, in addition to a significant pooled effect size in both groups, neurological disorders were associated with a marginally significantly greater impairment in ERN amplitude than addiction. Neurological disorders also presented shorter ERN latencies than addiction when compared with controls. The effect of Age as a moderator was in the expected direction, while no evidence was found for the influence of other moderators. The present findings can shed light on the 'addiction as a brain disease' debate. We suggest that, rather than a black-and-white position in this debate, a fruitful way forward is to quantify the degree of brain dysfunctions in addiction. And then examine to which extent the corresponding consequences preclude individuals' capacity to alter their drug-related behavior.

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Declarations of interest

None

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105127.

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