Age-related differences in the error-related negativity and error positivity in children and adolescents: a systematic review and meta-analysis protocol

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- 39 Conflict of interest: None.

Abstract

Background: The error-related negativity (ERN) and the error positivity (Pe) are electrophysiological signals linked to error processing, a crucial aspect of self-monitoring and regulation. Previous research suggests different developmental trajectories for the ERN and Pe, with the ERN increasing in strength during the course of childhood and adolescence, while the Pe appears to reach a plateau by late childhood. There are, however, reports that are discrepant with this pattern, and effects of participant, task and methodological characteristics are poorly understood. The main objectives of this systematic review and meta-analysis are to evaluate the effect of age on ERN and Pe magnitude in children and adolescents, and to examine potential moderators of these effects, including age, sex, experimental task, task difficulty, and topography and quantification of the ERN and Pe.

Methods/design: Studies that report group differences between age-groups or associations with age for the ERN and/or Pe magnitude in typically developing children and/or adolescents will be identified. The literature search will be conducted through PubMed and Scopus, all abstracts will be screened, and reference lists of relevant articles cross-checked for inclusion. The present protocol will also be disseminated on social media platforms to call for unpublished data. The data will be extracted from the eligible studies and will be included in random-effect meta-analyses in R. The results will include the estimation of age and age-group effect sizes, heterogeneity, risk of publication bias, and effects of moderating variables.

Discussion: The study will include a systematic literature search and meta-analyses to better understand age-related differences in the ERN and Pe magnitudes. The results will provide estimates of effect sizes that are relevant for calculating statistical power and sample sizes for future studies. In addition, it will provide benchmark effect sizes for typical development of the ERN and the Pe that could be used for comparison purposes in developmental studies of clinical or at-risk groups.

65 **Keywords:** Error-related negativity; error positivity; children; adolescents; development;
66 systematic review; meta-analysis; protocol.

Background

Neurocognitive development from childhood to adulthood involves improvements in self-monitoring and -regulation, increasingly allowing us to observe and adjust our thoughts, emotions, and actions in the service of our goals. A crucial element of these functions is the capacity to detect and react to errors, also known as error processing. The error-related negativity (ERN) and the error-positivity (Pe) are specific electrical brain signals that are detectable at the scalp with electroencephalography (EEG) time locked to errors. The ERN is a sharp negative deflection that peaks around 50-100 ms after an erroneous response, and has, among several theories, been considered a neural marker of conflict processing¹ or threat evaluation². The Pe is a positive deflection that peaks around 200-500 ms after an erroneous response, and has been suggested to reflect error awareness^{3,4}.

Many studies, predominantly cross-sectional studies, have investigated how these error components develop from childhood to young adulthood. The majority of the studies seem to indicate age-related differences of the ERN during development, with stronger magnitudes associated with older ages⁵, however, other results are inconsistent with this. Some studies support the notion of a continuous development of the ERN through childhood and into early adulthood⁶⁻¹⁰, while others do not¹¹⁻¹³. In contrast to the possibly protracted development of the ERN, the Pe has been suggested to mature at a relatively early age. The Pe has been reported to increase in strength in middle childhood¹², while other studies indicate that it has stabilized by late childhood^{10,13,14} (but see¹¹). Thus, it seems plausible that the ERN and the Pe have distinct developmental trajectories, with the Pe maturing earlier than the ERN.

We have a limited understanding of the effects of participant, task and methodological characteristics that could moderate the age effects on the ERN and Pe magnitude, although a recent meta-analytic review yielded partial support for main effects of sex and experimental task on the ERN¹⁵. Previous results have found larger ERN and Pe in males compared to

females in both adults¹⁶ and children¹⁵, but studies of sex differences in the effect of age in children and adolescents are lacking, limiting our understanding of the emergence of these differences¹⁷. It is possible that sex interacts with age as females show, on average, earlier pubertal maturation compared to boys^{18–20}, which might lead to sex differences in brain function²¹ and structure^{22,23}. Second, although the ERN and the Pe can be observed in multiple cognitive paradigms, including the Flanker task, the Go/No-Go task, Stroop and the Simon task^{5,24}, these paradigms yield task-dependent effects on the ERN and Pe^{15,24}, but it is not known whether the different tasks give different age-effects. Third, different paradigms or versions of the same paradigm may also differ in task difficulty, as evidenced by differences in the error rates, which is important to consider given that fewer errors are associated with larger ERN magnitude²⁵. Finally, there are multiple methodological differences in studies measuring the ERN and Pe^{12,17,26}. For example, the ERN and Pe can be measured via different forms of topographical analyses (e.g., single electrodes, average across several electrodes, decomposing brain activity), and there are several common methods to quantify the ERN and Pe (e.g., peak magnitude, peak-to-peak, mean difference between correct and error trials, or residuals), and these choices could lead to different results in studies of age-related differences^{27,28}. To conclude, we aim to investigate if the observed variation in participant (age and sex), task (paradigm and error rates) and methodological (topography and quantification) characteristics will moderate the age effect on the ERN and Pe.

The main objective of this systematic review and meta-analysis is to examine the effect of age on the ERN and Pe magnitude in typically developing children and adolescents, and to investigate potential moderators on these effects. We hypothesize greater ERN and Pe magnitudes with increasing age, however, we do expect the age-effect to be stronger for the ERN than for the Pe. We further expect the effect size of age on the ERN not to be moderated by age, indicating a linear and continuous development across childhood and adolescence.

However, we do anticipate the effect size of age on Pe to be moderated by age, reflecting developmental increases during middle childhood, followed by stabilization around late childhood. Finally, we aim to investigate a potential moderating effect of sex, experimental paradigm, error rate, topographic analysis, and quantification of the error components on the age-related effect size on the ERN and Pe.

Methods

Aims

We aim to examine the relationship between age and the ERN and Pe magnitude in the age-range from early childhood to young adulthood, and to identify possible moderating effects of age, sex, experimental task, task difficulty, topography and quantification of the ERN and Pe. We will conduct the meta-analysis based on healthy participants with no reported mental disorders or neurodevelopmental disorders. The present protocol is in agreement with the Preferred Reporting Items for Systematic reviews and Meta-analysis Protocols (PRISMA-P) guidelines²⁹ (Additional file 1).

Search strategy

We will conduct a systematic literature search to identify studies that are examining the development of ERN and/or Pe. The systematic literature search will be conducted using the PubMed and Scopus search engines. A pilot search was conducted in order to identify appropriate search terms in the search engines. Thus, the search will be based on the following search phrase: (“ERN” OR “error related negativity” OR “error negativity” OR “Pe” OR “error positivity”) AND (“child*” OR “adolescen*” OR “youth”) AND (“EEG” OR “electroencephalography” OR “ERP” OR “event-related potential”). Initially, after removing

duplicates, the abstracts will be screened for inclusion. Next, all eligible studies will be read in full and evaluated for inclusion by two authors (RB and CKT). As a final step, we will cross-reference relevant references of review articles and the included studies. In cases of disagreement regarding study eligibility, a decision will be made through discussion with the other authors. The systematic literature search is planned to be conducted in August 2020. We will also broadcast our protocol on social media channels, requesting relevant statistics from unpublished data that fulfils the inclusion criteria.

Inclusion and exclusion criteria

We will include all identified studies that are reporting associations between age and ERN and/or Pe magnitude. The eligibility criteria are: 1) original studies in English 2) published in peer reviewed journals 3) that reports the ERN/Pe in at least two cross sectional or longitudinal age groups or the correlation coefficient with age 4) in children and or adolescents (with participants < 18 years of age) 5) with no reported mental or neurodevelopmental disorders. If a study fulfils the inclusion criteria, but does not report enough information to estimate the effect sizes and variances, the corresponding authors will be contacted and asked if they can provide the missing data.

Moderators

To test whether age-related group differences or the age correlation varies across childhood and adolescence, i.e. whether there is evidence indicating non-linear developmental trajectories, in the ERN and/or Pe magnitude, we will test whether mean age has a moderating effect. To investigate potential sex by age interactions in the error components, we will aim to include sex as a moderator. Further, the included studies will likely vary in the experimental

task being used, task difficulty, topographic analysis, and quantification of the ERN and Pe. If possible, we will include these varying factors as moderating variables in the meta-analysis.

Extraction of relevant parameters

For studies comparing age-groups, we will extract means and variance measures for the ERN and/or Pe measurements and sample sizes for each age group. If the mean and standard deviations are not provided, we will extract relevant F or t statistics, if available. For correlation studies, we will extract correlation coefficients between age and ERN and/or PE measurements and sample size. For the analyses of moderators on the age effects, we will for each study extract the mean age in the full study sample or mean age for each age group in studies with group design. Further, we will extract the ERN and Pe magnitude for boys and girls, experimental task that was used, error rates of the experimental task as a measure of task difficulty, and the topographical analysis and quantification method used to quantify the ERN and Pe. Overview of the data extraction can be found in additional file 2.

Statistical analyses

All statistical analyses will be conducted in R, primarily using the “metafor”³⁰ package. Due to variation in samples and methodology, we will be using random-effects models (with a restricted maximum-likelihood estimator) to account for the variation in the true effects. For the studies that are reporting mean ERN and Pe magnitude across age groups (e.g., children vs. adolescents or children vs. adults), group, sex, experimental paradigm, topographic analysis and quantification of the error components will be treated as categorical moderators. The T^2 , a metric for inter-study variation, will be calculated for each of the age groups and the means will be compared using a two-tailed z-test. For studies reporting the correlation

coefficient between age and ERN/Pe magnitude, the correlations will undergo a Fisher's z-transformation and a meta-regression will be conducted to estimate the unstandardized regression coefficient. When reporting results, these statistics will be back-transformed to correlation coefficient values. In addition to the categorical variables, we will include linear age, quadratic age and mean error rates as continuous variables in the meta-regression.

Heterogeneity

To assess the heterogeneity of the effect sizes within the meta-analysis, the Q and I^2 statistics will be estimated and reported. The Q-statistic will indicate if the effect sizes between the studies are statistically different, while the I^2 -statistic will indicate the proportion of the observed variance that could be attributed to true effect sizes.

Statistically dependent effect sizes

Studies reporting more than one effect size on the same sample will result in statistically dependent effect sizes. For instance, longitudinal studies may report statistics for each timepoint, while cross sectional studies might report statistics for different conditions on the same sample. Both instances will report values that will covary either across time or experiment, which could bias the estimated effect size as dependent information is used at least two times. We will be using a three level meta analytic model to account for the dependency in the data.

Quality assessment (risk of bias)

We will calculate the statistical power of each study included in meta-analysis and compute the median statistical power using the ‘metameta’ R package (<https://github.com/dsquintana/metameta>), to assess the evidential value of each study and the overall summary effect size estimate. To evaluate the quality of the studies, all of the included studies will undergo a quality assessment based on publication guidelines, recommendations and checklist for EEG research^{28,31}.

Small study bias and publication bias

We will examine the potential for small study bias, which includes publication bias along with other forms of bias, through visual inspection of asymmetry in contour-enhanced Funnel plots, and Egger’s regression test. As the included studies might be characterised by small samples, we will use the p-uniform method to assess publication bias³² using the “puniform” package, if test assumptions are met (e.g., low heterogeneity) (<https://cran.rproject.org/web/packages/puniform/index.html>). We will additionally perform the test of excess significance³³ to determine if there are more statistically significant results than expected for a given sample of effect sizes and corresponding variances.

Discussion

The ERN and Pe are considered important electrophysiological components of error processing, and several original studies, mainly with cross-sectional designs, have aimed to investigate their developmental trajectory from childhood to young adulthood. On the one hand, several studies seem to indicate a protracted development of the ERN magnitude,

increasing in strength into late adolescence. On the other hand, Pe magnitude is thought to mature relatively early, and has been found to be stable from late childhood. However, there are also studies that are inconsistent with the abovementioned age-related patterns, and it is unclear if these developmental changes are influenced by participant, task and methodological characteristics.

The large majority of developmental studies on the ERN and Pe have been cross sectional and have included relatively small sample sizes. Cross sectional designs are highly influenced by individual differences and are not suitable to detect developmental trends within individuals over time. Small samples not only reduce the chance of detecting true effects that replicate, but also reduce the likelihood that a statistically significant result reflects a true effect, or can yield inflated effect sizes³⁴. Finally, the ERN has been considered to be a biomarker for anxiety³⁵, and potentially important also in relation to other mental disorders³⁶. However, in order to understand the transdiagnostic role of the ERN across mental disorders and their development, we first need an accurate understanding of typical developmental patterns. Thus, a thorough mapping of age-related effects on the ERN and Pe during normal development is highly needed. In addition, it is important to identify factors that modify the age-related effects on ERN and Pe magnitude to better understand the sources of variation in these patterns. To address some of these limitations, we aim to conduct a meta-analysis investigate age-related differences in the ERN and Pe magnitude in healthy children and adolescents, and to examine potential moderating effects of age, sex, experimental task, task difficulty, topographic analysis and quantification of the ERN and Pe.

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Additional File 1. PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)			
			Yes	No				
ADMINISTRATIVE INFORMATION								
Title								
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2			
Update	1b	If the protocol is for an update of a previous systematic review, identify as such			Not Applicable (NA)			
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract			NA			
Authors								
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	21-37			
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	13-16			
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments			NA			
Support								
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	18-19			
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	18-19			
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol			NA			
INTRODUCTION								
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	68-108			
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	111-121			

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	150-157
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	136 145-147 155-157
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	138-140
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	140-144
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	140-141 150-155
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	169-178
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	175-178
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	160-166
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	211-216 219-226
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	202-208
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	☒	☐	181-183 196-199
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	181-186 192-193
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☐	NA

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	219-226
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	211-216

Additional file 2. Data extraction form for individual studies**1. Identification of study**

1a. Study ID

1b. Authors

1c. Year of publication

1d. Title

1e. Journal title

1f. Digital object identifier (DOI)

2. Descriptive information about the study

2a. Design (Cross-sectional or longitudinal study)

2b. Sample size (and number of observations for longitudinal studies)

2c. Mean age and age-range

2d. Sex

3. Moderators

3a. Sample mean age

3b. Sex

3c. Experimental task

3d. Mean error rate (task difficulty)

3e. Topography (e.g., electrode, average across electrodes, independent component analysis)

3f. Quantification of the ERN and the Pe (e.g. peak amplitude, mean difference between correct and error trials, residuals)