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Event-related potential (ERP) measures of error processing as biomarkers of externalizing disorders: A narrative review

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ABSTRACT

Previous studies have shown that electrophysiological measures of error processing are affected in patients at risk or diagnosed with internalizing disorders, hence, suggesting that error processing could be a suitable biomarker for internalizing disorders. In this narrative review, we will evaluate studies that address the role of event-related potential (ERP) measures of error-processing in externalizing disorders and discuss to what extend these can be considered a biomarker for externalizing disorders. Currently, there is evidence for the notion that electrophysiological indices of error processing such as the error-related negativity (ERN) and error positivity (Pe) are reduced in individuals with substance use disorders, attention-deficit/hyperactivity disorder, and in forensic populations. However, it remains unclear whether this is also the case for other understudied disorders such as behavioral addiction. Furthermore, to fully understand how these deficits affect day to day behavior, we encourage research to focus on testing current theories and hypotheses of ERN and Pe. In addition, we argue that within an externalizing disorder, individual differences in error processing deficits may be related to prognosis and gender of the patient, methodological issues and presence of comorbidity. Next, we review studies that have related treatment trajectories with ERP measures of error processing, and we discuss the prospect of improving error processing as a treatment option. We conclude that ERP measures of error processing are candidate biomarkers for externalizing disorders, albeit we strongly urge researchers to continue looking into the predictive value of these measures in the etiology and treatment outcome through multi-method and longitudinal designs.

1. Introduction

The observation that some persons make more repeating mistakes than others was already a subject of study millennia ago by Roman philosophers such as Seneca the younger ("To err is human, to repeat error is of the devil") and Cicero ("Anyone can err, but only the fool persists in his fault"). These observations already constituted the idea that the persistence of making errors might be related to abnormal behavior. In modern times, the question why some people do not learn from their mistakes is still relevant and unanswered. The increasing knowledge about cognitive neuroscience can help to answer this question and enables us to investigate error processing by making use of modern psychophysiological techniques such as electroencephalography (EEG) and magnetic resonance imaging (MRI).

In the current paper we assume that the repeated making of errors is a common hallmark for externalizing behaviors, which are characterized by a pattern of inability to inhibit unwanted behaviors and properly adapt to new situations. Disorders within the externalizing spectrum traditionally include diagnosis such as attention-deficit/hyperactivity disorder (ADHD), substance use disorder (SUD), oppositional defiant disorder (ODD), conduct disorder (CD), and anti-social personality disorder (Krueger and South, 2009). Patients with these diagnoses share a variety of facets (e.g. impulsivity, irresponsibility) that relate to common behavior such as aggression and substance use (Krueger et al., 2007). In turn, these shared characteristics explain the proneness to maladaptive behaviors, such as risk-taking, un-empathic and delinquent behavior. Although this pattern can be both voluntary as well as involuntary, it could fit a pattern of not learning from these 'mistakes', or their experiences with negative outcomes. The cognitive processing of errors, i.e., the ability to detect and respond to a committed error (consciously or not), is an important regulating component in adjusting behavior and could thus be crucial for learning processes. It has been proposed (Olvet and Hajcak, 2008) that neurophysiological error processing is dysfunctional (i.e., reduced) in externalizing disorders and

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that this dysfunction is an etiological marker for these disorders. In this narrative review, we will explore and evaluate the empirical evidence for the hypothesis that reduced error processing, reflected as smaller error-related electrophysiological brain responses, could be a common biomarker for externalizing behavior and disorders.

Externalizing problems can cause tremendous harm to people displaying these behaviors, as well as to their environment and to society at large. Societal costs due to for example substance abuse, have been estimated to be more than $700 billion annually in the United States alone (Volkow et al., 2016). Treatment of patients with externalizing disorders has proven to be challenging, and is characterized by negative prognosis, treatment drop-out, high relapse rates, and increased chance of incarceration and recidivism. The origins of these externalizing disorders are often already observed in childhood and adolescence and continue or even aggravate later in life. Therefore, early identification of individuals at risk for developing an externalizing disorder and/or the identification of patients who are resistant to treatment might be helpful when tackling externalizing disorders. Investigating candidate biomarkers might be an important step in aiding to identify persons at risk or to further clarify pathophysiological mechanisms of these complex disorders.

There is a growing body of literature in search of candidate biomarkers for externalizing disorders and behaviors. There are several definitions for the term 'biological marker', but biomarkers generally refer to any objective characteristic that can be measured accurately, is reproducible and is sensitive and specific enough to be observed in a large heterogenous population from patients with a disorder as opposed to healthy individuals (Mehta et al., 2020). Neurobiological parameters, such as genes, hormones, skin-conductance, heart rate, and event-related potentials (ERP's), are examples of such biomarkers. Biomarker and endophenotypic research in the psychiatric and psychological field has greatly contributed to diagnostic and prognostic understanding of disorders and has identified provisional neuro-biological parameters that drive the etiology of disorders (Miller and Rockstroh, 2013). In turn, these markers can inform diagnostic tools, treatment options and future research. In the study of psychopathology, evidence suggests that ERP's are appropriate neurophysiological biomarkers (Hajcak et al., 2019). For example, dysfunction of the prefrontal cortex has been found in addiction (in magnetic resonance imaging studies; Goldstein and Volkow, 2011) and a diminished P300 in patients with substance abuse (Euser et al., 2012; Houston and Schlienz, 2018; Iacono and Malone, 2011) or with ADHD (Mehta et al., 2020). We can learn from the advances made in research on other neurophysiological biomarkers to pinpoint us what still needs to be done, such as investigating the role of genetic markers modulating error processing (e.g. Beste et al., 2010; Monoach and Agam, 2013) or investigating whether ERP's can be an index for behavioral change in treatment settings (Houston and Schlienz, 2018). In this review, we will focus on two response-locked EEG components as candidate electrophysiological biomarkers for error processing: the error-related negativity (ERN or Ne, Gehring et al., 1993, 2018; Falkenstein et al., 1991) and error positivity (Pe, Arbel and Donchin, 2009; Falkenstein et al., 1991; Overbeek et al., 2005). Here, we will not address behavioral performance nor other neurophysiological markers such as time-frequency theta or MRI measures and other behavioral related indices, such as reward processing. Where the ERN is an index for monitoring action outcome, the Pe can reflect error awareness and the more motivational significance of an error. Both ERP's serve as mechanistic markers for behavior adaptation. Research focusing on ERN and to a lesser extent on Pe, have revealed associations with psychological conditions. Previous reviews and meta-analyses (e.g., Gilian et al., 2017; Moser et al., 2016; Pasion and Barbosa, 2019; Riesel, 2019; Riesel et al., 2019), found that error processing can be affected in patients with internalizing conditions such as anxiety disorder and obsessive compulsive disorder, often evidenced by increased ERN potentials in patients compared to healthy controls. In the field of major depression disorder, inconsistencies of error processing effects still need to be resolved (Gilian et al., 2017). For instance, error related brain activity did not differ between healthy subjects and major depression patients in the study of Schrijvers et al. (2009) or was blunted in the study of Weinberg et al. (2016), yet ERN was related to symptom severity in patients in treatment of their depression (Schrijvers et al., 2009). In other studies, patients with depression disorder were more sensitive to error making reflected by an enhanced ERN compared to controls (Chi and Deldin, 2007; Moran et al., 2017). Similarly, the ERN seems to be a suitable biomarker for anxiety in children and adolescents (Hanna et al., 2020; Meyer, 2017).

This narrative review will not provide a systematic overview of ERN and Pe studies in externalizing disorders. Instead, we take a step back from previous findings and discuss the current state of the art for the notion that reduced ERN and Pe are neurophysiological biomarkers for externalizing disorders by answering the following questions: 1) What is the evidence that the ERN/Pe is reduced in externalizing populations? 2) Can a reduced ERN/Pe be a predictor of externalizing disorders? 3) Are there individual differences in ERN/Pe amplitudes within externalizing disorder populations, and what do these individual differences indicate? 4) Can the ERN/Pe be indicative of treatment trajectories? 5) Can error processing be improved by targeted interventions?

2. What is the evidence that the ERN/Pe is reduced in externalizing populations?

To investigate biomarkers is to explore deficits or sensitivities in comparing patient samples and healthy individuals. There are several case-control studies showing that ERN and Pe are reduced among externalizing populations (e.g., Brazil et al., 2009; Marquardt et al., 2018; Morie et al., 2014). In these studies, the typical design is to contrast the amplitude of the ERP's, measured by a typical cognitive task such as the Eriksen Flanker or Go-noGo task, between the clinical and control groups. The robustness of the reduced ERN and Pe in externalizing populations has been very recently confirmed by two meta-analyses compiling case-control studies (Lutz et al., submitted; Pasion and Barbosa, 2019). The meta-analysis of Pasion and Barbosa (2019) found an overall effect size of $g = -0.65$ (based on 32 ERN studies, 44 effect sizes, $n = 1921$), where a negative g indicates a decreased amplitude for the clinical/subclinical group. Similarly, Lutz et al. (submitted) found a small to medium effect for the ERN and Pe, observing a decreased amplitude for the clinical/subclinical group when compared to healthy controls. These studies provide the initial evidence for reduced ERN and Pe in specific subgroups within the externalizing spectrum, i.e., substance use disorder, ADHD and personality disorders, as well as in individuals with subclinical levels of externalizing behavioral problems (e.g., symptoms of aggression, psychopathy, and impulsivity, Hall et al., 2007; Zijlmans et al., 2019). Also, in the two meta-analyses, several important moderators, such as ERN peak scoring, type of diagnosis, disorder severity, task and presence of comorbidity and performance feedback and age, were tested to elucidate on the heterogeneity of the data. Although these meta-analyses differ in inclusion criteria and approach, the results of the meta-analyses highlight that performance monitoring processes are indeed compromised in individuals on the externalizing spectrum. This is in correspondence with results from disorder-specific systematic reviews on error processing, such as the meta-analysis of Geburek et al. (2013) and Kaiser et al. (2020) in ADHD and the systematic review of Luijten et al. (2014) on substance use disorders. In sum, evidence is building to support the hypothesis that reduced error processing, indexed by the ERN and Pe, is present in externalizing disorders and could indeed be considered a suitable biomarker.

When gathering the evidence for the ERN and Pe as a neurobiomarker in the externalizing spectrum, we have to consider possible moderators, that are for instance population or research related. When looking at the patients with externalizing disorder, sex is a possible moderator. In healthy samples, performance monitoring at a behavioral and neurophysiological level is moderated by sex (Fischer et al., 2016; Hill et al., 2018; Larson et al., 2011; Li et al., 2009). That is, it appears that men show more error related activity than females (Fischer et al., 2016; Hill et al., 2018) and that women show different activation and deactivation patterns of the brain than men (Li et al., 2009). This could be due to sex related morphometric differences of the brain, e.g. a larger anterior cingulate cortex (ACC) in men (Ruigrok et al., 2014). It is known that disorders in the externalizing spectrum are more prevalent in males (Becker and Hu, 2008; Eaton et al., 2012; Krueger and South, 2009) which is reflected in the unbalanced sampling of the (sub)clinical participants in error processing studies. Including participants in studies of both sexes appears to be challenging, making it not yet possible to draw solid conclusions when systematically investigating error processing deficits between male and female patients, as Kaiser et al. (2020) rightfully discuss in their ERP meta-analysis in ADHD. Already, there are indications that error processing is affected differently for males than females in externalizing samples (for psychopathy see Efferson and Glenn, 2018; in internet gaming disorder; Dong et al., 2018; for food addiction see Hsu et al., 2017). For instance, when predicting cocaine relapse and early relapse time, a reduced activity in the dACC and thalamus was indicative for females, whereas the reduced activity in the dACC (dorsal anterior cingulate cortex) and left insula was indicative for males (Luo et al., 2013). More extensive research with this moderator is warranted to pinpoint which brain area and activity is affected for males or females in particular, and whether this is disorder specific or generalizable for the externalizing spectrum.

Another possible moderator that should be taken into account when studying error processing pertains to methodological choices in ERP (pre)processing. Recently, Klawohn et al. (2020) investigated the effect of different quantification ERP methods, and although there are differences, most methods had acceptable to good internal consistencies. Indeed, there are several important moderators in error processing studies that affect the internal consistencies of studies (Sandre et al., 2020), carefully investigated in the meta-analysis of Clayson (2020). Choices relating to EEG referencing, the scoring procedure, electrode (cluster), (ocular) artifact rejection and number of trials for ERP calculation, can influence the internal consistency of the ERN (Clayson, 2020). An adequate solution for this moderation issue in EEG research is the disclosure of hypotheses, data collection, processing and analyses through pre-registration (Paul et al., 2021) and open science practices, which not only allows for reproducibility and transparency but provides a control mechanism for these possible moderators.

In order to further validate whether neurophysiological markers of error processing are suitable as biomarkers of externalizing disorders, we need to better understand how defiant error-related brain activity acts as an underlying mechanism in these disorders. The functional significance of error processing relies on several theories or hypotheses that might be complementary and exclusive at the same time. The mismatch, reinforcement and learning based, conflict monitoring and motivational significance theory, as outlined in Olvet and Hajcak (2008) and Weinberg et al. (2012) for ERN and the affective-processing, behavior-adaptation and error awareness hypotheses, as discussed in Overbeek et al. (2005) for Pe, could help us to understand the underlying mechanisms for the disruptive behavior of patients with externalizing disorders. Briefly, these hypotheses attempt to explain how errors are (not) processed and evaluated by the brain, how errors elicit learning behavior which in turn leads to adjustment in behavior. When this system does not adequately work, error processing is affected and leads to the inability to adjust disadvantageous behavior, which is often observed in individuals with externalizing disorders. However, it is unclear how these hypotheses explain day to day behavior that we see in patients with externalizing disorders or, how we could use these hypotheses to improve error processing deficits (e.g. training performance monitoring using feedback or error awareness training).

A continuation of exploring the neural network behind performance monitoring is encouraged (Wessel, 2012; Wessel et al., 2012). For instance, an insufficiently working salience network of the brain, indicated by hypoactivity of the insula or ACC (as described in Ham et al., 2013) can explain the performance deficits seen in externalizing disorders. Also, the interplay of ACC and other brain regions on functional and structural level contributing to regulating behavior, cannot be omitted. For instance, distinct activation patterns of the insula, rostralACC and the dorsolateral prefrontal cortex in patients with cocaine addiction and intermittent explosive disorder (Moeller et al., 2014a, 2014b) explained the behavior in the performance tasks.

So far, we interpreted reduced error related brain activity as an indicator of the inability to adjust behavior to avoid future errors, which in turn are related to symptoms (e.g. the continuation of substance abuse: Crane et al., 2018; Easdon et al., 2005; Franken et al., 2007; Hajcak, 2012; Luijten et al., 2011; Sokhadze et al., 2008). The late component of error processing, Pe, has only recently been subject of experimental studies (e.g., Di Gregorio et al., 2018), and therefore less is known about the functional significance of the Pe in externalizing disorders. In the study of Rosburg et al. (2018), it has been proposed that a reduced Pe could reflect the reduced awareness of the committed errors in child sexual offenders, which in turn could contribute to their delinquent behavior. A reduction in the recognition (that is the awareness) of, or the motivational significance of an error, might explain why individuals with externalizing disorders are less inclined to change their behavior because of that error. Clearly, more studies are needed to clarify the role of the reduced ERN and Pe in externalizing conditions. One interesting possibility, that has become available with mobile EEG and mobile cognitive assessments, is the investigation of error-processing in ‘daily life’, particularly in relation to externalizing behaviors. With this method, we could gain knowledge about the significance of error processing deficits in daily cognitive processes.

Another outstanding question is whether the ERN and Pe are suitable biomarkers for the externalizing spectrum or whether it is specific to certain externalizing disorders or problem behaviors. There is a substantial number of studies providing evidence that error processing is affected in individuals with ADHD or in substance use disorder. However, other externalizing conditions have been understudied, such as anti-social personality disorder or psychopathy (Vallet et al., 2021). A few incidental case-control studies have indicated that error processing is reduced in behavioral addictions, in for example computer gaming addiction (for the ERN, Littel et al., 2012) or internet gaming addiction (Park et al., 2020; Zhou et al., 2013), and food addiction (Franken et al., 2018). Taken from these four studies, the participants with addictive behavior made more errors, were more impulsive, and showed decreased ERN, indicating to reduced reduce performance monitoring. Although these results are in accordance with results from substance addiction, we cannot yet draw firm conclusions based on four studies. Yet, we have reasons to believe that future studies will find error processing deficits in patients with behavioral addiction as brain studies examining the functional activity, structure, and connectivity already have shown that the ACC or orbitofrontal cortex and connectivity with the insula are affected (for instance in internet gaming disorder: Dong et al., 2015; Ko et al., 2014; Lee et al., 2018; Xing et al., 2014; Zhou et al., 2011). More research is needed on both ERN and Pe in diverse externalizing populations to explore whether the two ERP's are a general biomarker for externalizing disorders, or only related to specific externalizing behaviors.

Another outstanding and relevant issue is the role of error processing in explaining comorbidity as externalizing and internalizing conditions can co-occur (Krueger and Markon, 2006). Since externalizing disorders are often characterized by a decreased ERN and internalizing disorders by an increased ERN, it is interesting to investigate how error processing plays a role in comorbid conditions (as for example investigated in the study of Schellekens et al., 2010 and Gorka et al., 2016). Although it has been proposed that error processing can be considered as a transdiagnostic marker which is also relevant for individuals presenting with comorbid disorders (Ladouceur, 2016; Pasion and Barbosa, 2019;

Weinberg et al., 2015), the direction of the association (reduced vs. increased) is one important aspect that needs to be examined. When trying to understand the comorbidity issue, the *p* factor or a generalized psychopathology factor might offer insight (Caspi et al., 2014; Caspi and Moffitt, 2018). The *p* factor, incorporating the internalizing and externalizing and thought disorders/psychotic experiences allows for the co-occurrence of problems from all disorders, which is applicable in our discussion here. However, until now researchers have been devoted to test such nosology in large populations, and a few studies have validated this model with global executive functioning in children (Bloemen et al., 2018; Martel et al., 2017; Shiels et al., 2019). We can only speculate how error processing or cognitive control fits in the general factor. The error processing effects found in both internalizing and externalizing disorders support the fundamental idea of the bifactor or hierarchical factor, proposed by Caspi and Moffitt (2018). It is therefore important that error processing components are incorporated in the Research Domain Criteria of the NIMH (as discussed in Weinberg et al., 2015). For now, experimental studies are needed to investigate the role of error processing in the etiology of either externalizing or internalizing disorders as well as comorbidity between these disorders by controlling for both symptoms in terms of onset, severity, and genetic predispositions.

3. Is reduced ERN/Pe a predictor of externalizing disorders?

In order to be able to determine whether reductions of the ERN/Pe can be considered an etiological biomarker for externalizing disorders, the role of error processing should be studied at an early age. When establishing deficits in adulthood, the notion that error processing was already affected in childhood, should be tested. Several cross-sectional or case-control reports have found reduced error processing in children with elevated subclinical levels of externalizing behavioral problems and children with clinical externalizing disorders (e.g., Burgio-Murphy et al., 2007; Kessel et al., 2016; Meyer and Klein, 2018; Moadab et al., 2010; Stieben et al., 2007) and ADHD (Groen et al., 2008; Senderecka et al., 2012). The next step is to test these associations in longitudinal designs in children and adolescents, as illustrated by the review study of Meyer (2017) in anxiety. These designs should keep in mind the normal trajectory of error processing indices (such as the increase of the ERN over time found in the reviews of Lo, 2018, and Tamnes et al., 2013) but are essential to determine whether error processing could be a predictor for externalizing problems.

Case-control studies do not provide information about the causal role of error processing deficits in externalizing disorders. It has been proposed that error processing deficits could indeed be one of the causal factors of externalizing disorders. To study this, the level of error processing in at-risk samples (that is children, family members, or adults that have an increased chance for developing externalizing problems due to their parental conditions or exposure) can indicate a possible causal effect. The study of Euser et al. (2013) is an example of such a study, where the hypothesis that error processing is an antecedent and reflects biological predisposition to the disorder (in this case SUD). High risk adolescents, who had a parent undergoing treatment for SUD showed smaller ERN amplitudes than normal risks (healthy controls). In this design, one can find evidence whether the deficits found in error processing contribute to the disorder that is diagnosed at a later stage in their lives. This idea has been studied previously with other candidate neurophysiological markers such as the reduced P3 (Euser et al., 2012; Iacono et al., 2002) within the externalizing spectrum. One the other hand, it is also conceivable that error processing deficits could be a consequence of psychopathology. This implies that error processing deficits are not yet detectable at the beginning of a disorder, but rather a result of the disorder. This could also clarify why certain patients show a negative prognosis as opposed to others. This alternative hypothesis seems to be particularly relevant in substance use disorders, as it is known that the prolonged use of substances has detrimental effects on the brain and cognitive functions (Goldstein and Volkow, 2002, 2011; Leshner, 2003).

To conclude, there is some evidence of early error processing deficits in children in the externalizing spectrum. It remains unclear whether error processing deficits can be considered a vulnerability or consequence of developing externalizing disorders. Since experimental studies addressing causality issues are obviously unethical, more prospective longitudinal cohort studies focused on the ERN and Pe and the development of externalizing problems over time among children in the general population are needed in order to gain insight in developmental aspects and their causal role in problem behaviors.

4. Are there individual differences in ERN/Pe amplitudes within externalizing disorder populations, and what do these individual differences indicate?

Both meta-analyses mentioned previously (Lutz et al., submitted; Pasion and Barbosa, 2019) have shown that there is substantial heterogeneity within clinical groups, indicating that error processing deficits may not be evident for all patients within a clinical disorder and are present in various degrees. There are several possible explanations for the observed variation in the error processing correlates, such as individual differences, presence of comorbidity, severity of symptomatology. First, variability in ERN could be due to individual differences in several domains. For instance, there is evidence that the individual levels of cognitive control in patients with ADHD (Meyer and Hajcak, 2019) and the individual levels of the trait defense reactivity (Weinberg et al., 2012) can modulate the ERN. Several other studies have shed light on additional characteristics that modulate ERN/Pe, such as working memory performance (Miller et al., 2012), fearfulness in toddlerhood (Brooker and Buss, 2014), sensitivity towards rewards and punishment (Boksem et al., 2006; Dikman and Allen, 2000), personality or externalizing traits (Pailing and Segalowitz, 2004; McDonald et al., 2021) and behavioral inhibition (Amodio et al., 2007). Also, it is important to mention that the role of individual differences needs to be studied in large samples. Small sample sizes, typically used in these studies, overestimate effect sizes and have low reproducibility (Button et al., 2013; Larson and Carbine, 2017). An example of this is point is illustrated in the study of Bernoster et al. (2019). In this larger scale study, a clear link between ERN and impulsivity was not found, despite previous reports of this association in smaller scale experiments. The role of individual differences in error processing clearly merits further investigation as it could explain the heterogeneity of the error processing deficits. Another possible explanation for the variation within clinical groups is the presence of comorbid internalizing problems, that often co-occur in for example substance use disorders (Franken et al., 2017; Olvet and Hajcak, 2008; Smith et al., 2017). Or, variability in error processing deficits could be due to the severity of the externalizing symptoms. Both relate to a more dimensional approach of externalizing spectrum, as suggested by Krueger et al. (2007). The high or low levels of externalizing and comorbid problems (irrespective of a particular disorder) are related to more or less pronounced error processing and other executive functioning deficits, can explain possible variance observed. In turn, studying this link can be insightful for the global functioning of patients. Already, studies have examined the degree of symptomatology and its association with the variation in ERN or Pe. For instance, a smaller ERN has been related to more heavy heroin use (Chen et al., 2013), alcohol use (Campanella et al., 2017; Smith and Mattick, 2013), and nicotine dependence (Luijten et al., 2011).

To investigate the comorbidity, symptom severity and global functioning hypotheses, experiments could use ecological momentary assessment applications to asses error processing in combination with comorbid symptoms, symptom severity or functioning ratings in patients. This line of research should be continued and include the Pe component, in order to examine whether and how error processing is related to individual differences, symptom severity, or global functioning in externalizing patients. This knowledge could aid in predicting prognosis of patients and give insight in treatment success.

5. Can error processing be indicative of treatment trajectories?

In line with the previous paragraph, discussing the ERN or Pe as an index of symptom severity, error processing could be used as an indicator of status, relapse or treatment success in externalizing disorders (Gorka et al., 2019; Marhe et al., 2013, Steele et al., 2014, and at trend level in Luijten et al., 2016). The study of Gorka et al. (2019) showed that the ERN can possibly be related to pathological stages of patients with alcohol use disorder. In other words, the magnitude of the ERN could differentiate between current, remitted and at-risk in patients with alcohol use disorder. Similarly, although at trend levels, Pe and ERN were related to smoking relapse and resumption in Luijten et al. (2016). Both these studies give insights in how error processing could be directly related to recovery trajectories in addiction disorders. When investigating treatment success, the results of Marhe et al. (2013) and Steele et al. (2014) showed how error processing deficits could be predictive of treatment outcome, by relating error related brain activity to later treatment success. Moreover, the results of Padilla et al. (2011), Schlienz et al. (2013) and Schlienz and Hawk (2017) suggest that ERN is very sensitive to the cessation of alcohol in patients with alcohol disorder. Indeed, distinct activation patterns during error processing of dACC, thalamus, and insula in cognitive processing are found during abstinence in other addiction disorders, such as cocaine-dependency patients, implying that indicators of brain functionality are of predictive value for drug relapse (Connolly et al., 2012; Luo et al., 2013). Indications of the predictive value of error processing for treatment outcome are also found in research in forensic settings. For example, Steele et al. (2015) found that Pe could differentiate between incarcerated males who were or were not subsequently rearrested. In this prospective study, the error related brain activity of adult men was related to later rearrests, information that was gathered in a follow-up. Although several studies show that error processing is potentially predictive of treatment outcome, more evidence is needed to determine its potential in other externalizing disorders.

6. Can error processing be improved by targeted interventions?

At the moment, the improvement of (aspects of) cognitive control, such as error processing, is one of the crucial targets in many studies aiming to treat externalizing disorders. However, in practice it seems rather difficult to improve cognitive control. With exemption of one study (Schoenberg et al., 2014), we are not aware of studies showing that certain treatments can improve error-processing (reflected by improvements in ERN/Pe amplitudes post interventions) specifically, nor that improvements in error processing result in adaptations in behavior. Having said this, there have been successful attempts in the broad area of self-control (Inzlicht et al., 2014) that provide important clues on how to continue the search for effective interventions to improve error processing. Broadly, these studies focus on three types of interventions: cognitive-behavioral training, brain stimulation (Bellaïche et al., 2013; Carmi et al., 2018; Verveer et al., 2021), and meditation techniques (Slagter et al., 2011). Cognitive-behavioral therapy could address elements that are related to cognitive processes. An interesting attempt to test this idea is the study of Schoenberg et al. (2014), where cognitive therapy addressed cognitive flexibility, attention, and behavioral regulation. In this study, they found that mindfulness-based cognitive therapy elevated Pe in adult patients with ADHD. Concerning brain stimulation, current randomized control trials and experiments are exploring the possibility of using brain stimulation to modify cognitive control and neurofeedback to adjust performance monitoring. Non-invasive neurostimulation using transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) can alter the activity of targeted brain regions, associated with error processing, such as the ACC. Although research of the use of neurostimulation in externalizing disorders is accumulating and promising (for drug addiction: Song et al., 2019; in ADHD: Soltaninejad et al., 2019), very few studies investigate its effects on cognitive control and even less studies investigate error processing specifically. In healthy volunteers, successful attempts to modulate error processing through tDCS have been reported (Bellaïche et al., 2013). There are preliminary indications that TMS treatment is related to changes in ERN in patients with obsession-compulsive disorder (e.g., Carmi et al., 2018). However, in patients with cocaine addiction that underwent tDCS treatment (Verveer et al., 2021), no changes in the ERN nor craving were found. Last, meditation techniques are another promising avenue to improve cognitive control. Researchers are currently exploring its effects in healthy volunteers (Andreu et al., 2019; Lin et al., 2019; Pozuelos et al., 2019; Quaglia et al., 2019; Saunders et al., 2016; Slagter et al., 2011; Teper et al., 2013) and it seems too early to speculate about the effectiveness in general and for externalizing disorders in particular.

At the moment there are no proven interventions that could indicate that error processing could be improved in patients with externalizing disorders, but cognitive training, particularly like the study of Schoenberg et al. (2014), brain stimulation, and meditation techniques are certainly worth exploring, as they can address cognitive control elements shown in studies with healthy samples. Despite the limitation that improving error processing will only alleviate some of the problems seen in patients with externalizing disorders, future research should investigate whether improving error processing in turn leads to adapting their behavior.

7. Conclusion and future directions

Our narrative review shows that error processing and specifically a reduced ERN and Pe are associated with externalizing symptoms, and that empirical evidence is building that deficits in error processing measured at neurophysiological level might be a suitable biomarkers for externalizing conditions. However, many questions remain unanswered. We address several key themes in Table 1, where we give an overview of preliminary evidence and recommendations for future research directions. In this review, we focused on the neurophysiological indices of error processing (ERN and Pe), leaving the discussion on the significance of behavioral indices of error processing untouched. Also, a related ERP, the P300, shares important variance with ERN/Pe, and we would like to shortly touch upon these topics.

Concerning the functional significance of the ERP measures, there are some indications that ERN or Pe is related to task behavior and behavioral adjustment. For instance, the Pe was correlated with post-error slowing (PES; Hajcak et al., 2003; Nieuwenhuis et al., 2001). Additionally, the ERN is associated with post-error accuracy, when mediated by post-error slowing (Beatty et al., 2020). Although there is no consensus yet, several studies (e.g. Cavanagh et al., 2009; Kalfaoğlu et al., 2018) have found relationships between ERN and post-error slowing, indicating that ERN is related to task-related behavior. The authors in Beatty et al. (2020) carefully laid out possible explanations for the inconsistencies around the relationship between behavior and ERN. In addition, it is not clear to what degree the behavioral performance during error processing tasks is affected in patients with externalizing disorders. For example, post-error slowing appears to be affected in patients with ADHD (Balogh and Czobor, 2014) and cocaine use disorder (Franken et al., 2007). On the other hand, there are reports showing a distinct pattern of behavior. For instance, the externalization groups in the study of Gorka et al. (2019) not make more errors in cognitive tasks, nor do they take longer (evidenced in reaction times) in pressing the correct buttons when compared to controls, as in the study of Zhang et al. (2009) in children with ADHD. Studying the significance of behavioral performance during error processing as well as the association of the behavior with the neurophysiological indices is encouraged. Elucidating on this could answer another interesting question: how ecological valid are our lab measures of error-processing when

Table 1
Table with key formulations from this review, a short overview of evidence and suggestions for future directions.

Key formulations	Preliminary evidence[a]	Future research directions
Psychometric characteristics of the error-related negativity are clear	Sandre et al. (2020) Klawohn et al. (2020) Riesel et al. (2013) Rietdijk et al. (2014) Clayson (2020)	Report and examine the role of moderators, such as gender and methodological decisions, in ERN/Pe experiments.
Error-related negativity and error positivity is reduced in patients with externalizing disorders	Lutz et al. (submitted) Pasion and Barbosa (2019) Kaiser et al. (in ADHD: 2020) Vallet et al. (2021)	- Extend knowledge of the underlying theories for ERN and functional hypotheses of Pe - Investigate whether error processing is affected in behavioral addiction
Cause or effect of error processing in psychopathology unclear	Meyer (2017) Euser et al. (2013)	Investigating the developmental path of error processing in relation to psychopathology through longitudinal and cross-lagged model designs
Error processing is related to individual differences in the cognitive and personality domains, disorder severity and comorbidity	Cognitive/ personality domains: Pailing and Segalowitz (2014) Reward/ Punishment sensitivity: Boksem et al. (2006) Symptom severity: Campanella et al. (2017) Comorbidity: Franken et al. (2017)	Studying moderating measures to explain heterogeneity in disorders in larger samples - Symptom severity - Relation to comorbidity - Traits and personality - Genes and hormones - Other cognitive measures (e.g. working memory, attentional bias) - Error processing in daily life; using ecological momentary assessments tools
Error processing could be used as an indicator of status, relapse or treatment success	Gorka et al. (2019) Marhe et al. (2013) Steele et al. (2014) Luo et al. (2013) Steele et al. (2015)	Prospective studies using neuroprediction: examining the predictive value of error processing for treatment trajectory and relapse/ rearrests rates
Unclear whether and how we can train or stimulate performance monitoring to reduce error processing deficits	Schoenberg et al. (2014) Bellaïche et al. (2013) Verveer et al. (2021)	Through training programs, stimulation techniques or new experimental paradigms, can we improve error processing deficits?

[a] The authors acknowledge that more studies than mentioned here support the key formulations drawn.

translating to real-life behavior? We recommend researchers to endeavor in elucidating this through e.g., ecological momentary assessment and virtual reality techniques, in order to better test these hypotheses.

The reduced P300 has been considered a viable predictor for externalizing disorders (see e.g., Patrick et al., 2006). There are however obvious paradigm/component related differences with the reduced ERN/Pe, such as the polarity, latency (ERN) and onset. The latter characteristic differentiates the ERP's the most: the ERN/Pe is triggered by errors (response triggered) whereas the P300 is elicited by a scope of stimuli: affective, oddball etc.. Hence, the P300 reflects broader processes of decision making, leaving the unique feature of ERN and Pe to be specific error processing ERP's. Together these ERP's, among other ERP's such as N200, predict neurocognitive processes and behavior for externalizing disorders.

Most studies in this research area consist of relatively small case-control samples, in predominantly ADHD and SUD which limits our knowledge on the actual role of error processing. It should be examined whether the variation in error processing found within externalizing disorders is related to differences individuals and their psychopathology. Case-control studies cannot solve questions such as ‘is reduced cognitive control a cause or consequence of externalizing disorders?’ and ‘can we improve error processing in order to help individuals with externalizing problems?’. Future studies should focus on developmental processes in order to clarify a possible causal role, by using longitudinal designs and by exploring the effect of error processing on daily behavior. Also, more studies on the clinical relevance and development of intervention programs to improve error processing in externalizing disorders are needed. We believe that multi-method studies on error processing that are embedded within cognitive neuroscience (MRI, EEG), epidemiology (large prospective cohort study), and the emerging area of ecological momentary assessments (EMA), will be a fruitful new avenue to further explore mechanisms, treatment, and prevention of externalizing disorders.

CRediT authorship contribution statement

IF provided the rationale for this manuscript. ML wrote the manuscript with input of IF, RK commented. All authors significantly contributed to the editing of the manuscript and have approved the final manuscript.

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Declaration of competing interest

The authors declare that they have no conflict of interest.

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