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Review article

Beyond a blunted ERN - Biobehavioral correlates of performance monitoring in schizophrenia

H. Kirschner [a,*], T.A. Klein [a,b,*]

[a] Institute of Psychology, Otto-von-Guericke University, D-39106, Magdeburg, Germany
[b] Center for Behavioral Brain Sciences, D-39106, Magdeburg, Germany

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ABSTRACT

Cognitive deficits are well documented in schizophrenia. Here, we reviewed alterations in performance monitoring as potential marker of cognitive deficits in schizophrenia. We found that performance monitoring alterations in schizophrenia are specific to early (indexed by blunted error-related negativity (ERN)) and late (reflected in blunted error positivity (Pe)) internal error processing, while external performance feedback processing in simple response feedback tasks is relatively preserved. We propose, that these performance monitoring deficits may best be interpret as one aspect of disrupted theta band (4−8 Hz) oscillations over medial frontal recordings sites. Midfrontal theta dynamics are an increasingly established direct neural index of the recruitment of cognitive control and are impaired in several clinical populations. While theta-related ERPs (the ERN) may be an easy to assess marker of cognitive deficits in schizophrenia, further work investigating the trial-by-trial dynamics of theta in both the time and time-frequency domain is needed to parse cognitive deficits in schizophrenia into finer levels of detail and evaluate theta modulation as a therapeutic tool.

1. General introduction

Cognitive and intellectual underperformance is at the core of many psychiatric conditions, such as schizophrenia. Hence, there is an urgent demand to identify reliable markers of and mechanisms that contribute to impaired cognitive functioning to refine diagnosis and to inform targeted interventions. In the following, we will review biobehavioral correlates of performance monitoring (PM) as a potential key mechanism that contributes to cognitive deficits in schizophrenia.

1.1. Cognitive deficits in schizophrenia

Schizophrenia is a severe psychiatric condition with a heterogeneous combination of symptoms. Typically, these symptoms can be divided into 'positive', 'negative' and 'cognitive' categories (Kahn et al., 2015), which we will briefly describe in the following: Positive symptoms can be characterized as behavior and thoughts that are not normally present. These symptoms are typically referred to as recurrent psychosis, which is the loss of contact with reality. Psychosis consists of delusions, hallucinations and disorganized speech and behavior. Negative symptoms include affective flattening, social withdrawal, anhedonia, and diminished initiative and energy. Cognitive symptoms in schizophrenia are characterized by a variety of cognitive dysfunctions (American Psychiatric Association, 2013; Kahn et al., 2015).

While in the past, schizophrenia was mainly defined by its psychotic symptoms, there is a push in the field to position schizophrenia primarily as a cognitive illness (Kahn and Keefe, 2013). Kahn and Keefe (2013) argue that the emphasis on psychosis in the diagnosis and treatment of schizophrenia has precluded the development of adequate treatments targeted at cognitive deficits. Indeed, research suggests, that cognitive impairment in schizophrenia strongly predicts poor functional outcomes (e.g., Strassnig et al., 2015) and that this association is mediated by negative symptoms (Ventura et al., 2009). However, effective treatments for cognitive impairment and negative symptoms are lacking (Fusar-Poli et al., 2015; Insel, 2010).

Executive functioning is among the cognitive domains most impaired in schizophrenia (Reichenberg et al., 2009). Executive functioning (often also called cognitive control in the psychological literature) refers to a set of processes involved in adaptive, goal-directed behavior and involves a broad set of brain regions (e.g., prefrontal cortex, pMFC) and multiple neuromodulators (e.g., dopamine, glutamate). In this review we focus on performance monitoring as a proposed mechanism of

* Corresponding authors at: Institute of Psychology, Otto-von-Guericke University, D-39106, Magdeburg, Germany.
E-mail addresses: hans.kirschner@ovgu.de (H. Kirschner), tilmann.klein@ovgu.de (T.A. Klein).

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impaired executive functioning in schizophrenia, that is distinguishable from other aspects of executive function that are impaired in schizophrenia (Kerns et al., 2008).

1.2. Performance monitoring – a summary

Human performance monitoring encompasses error detection, evaluation of performance outcomes and consequent behavioral adjustments and is therefore essential for adaptive, goal-directed behavior (Ullsperger et al., 2014b). Adaptive behavior in this context can be understood as the result of a continuous feedback loop: During and after an action, the brain's performance monitoring system monitors for events indicating that outcomes and the states of the organism and its environment deviate from the desired goals (i.e., whether there is an error in predicting an action outcome). This information (the so-called prediction error) is used to signal the necessity and magnitude, and perhaps the type of adaptations that aim at compensating the problem and at optimizing actions in similar situations in the future (see also Fig. 1). Neuroimaging studies have consistently implicated the posterior medial frontal cortex (pMFC), in particular the anterior midcingulate cortex in this monitoring and signaling function (Ridderinkhof et al., 2004; Ullsperger et al., 2014a). Using human electroencephalography (EEG) various studies demonstrated that action errors and negative feedback elicit a stereotypical event-related potential (ERP) sequence associated with performance monitoring: a fronto-central negativity followed by a central-parietal positivity (Ullsperger et al., 2014b). After action errors in simple reaction time task, a fronto-central error related negativity peaking around 50–100 ms (called the ERN or Ne; Falkenstein et al., 1991; Gehring et al., 1993) is followed by a centro-parietal error positivity (Pe) occurring 200–500 ms after incorrect responses (named the Pe; Falkenstein et al., 2000). Interestingly, a small negativity in the time window of the ERN can be observed after correct responses as well (the correct-related negativity (CRN); Vidal et al., 2000). While the underlying mechanisms of the ERN are still debated, at least two major accounts have been put forward. They suggest that the ERN reflects the detection of post-response conflict or prediction error signals (for review, see Ullsperger et al., 2014b). The Pe has consistently been associated with the emergence of error awareness and confidence in subjective error judgements (Boldt and Yeung, 2015; Endrass et al., 2007; Kirschner et al., 2020; Murphy et al., 2012). In situations where we have to rely on feedback to evaluate actions, negative feedback is followed by a negativity (named the "feedback-related negativity FRN; Miltner et al., 1997; Walsh and Anderson, 2012) and a subsequent positivity (the P300; Polich, 2007). The FRN peaks 200–300 ms after performance feedback and is thought to index consummatory neural activity (as opposed to anticipation) thereby allowing an initial evaluation of action outcomes and associated attention allocation. The FRN is followed by the P300 ERP component which reflects orienting and memory updating (Polich, 2007). In the time-frequency space the EEG activity described above is reflected in increased mid-frontal theta activity (i.e., neural oscillations in the theta band (4–8 Hz) over medial frontal recording sites), which is thought to indicate the recruitment of cognitive control (Cavanagh and Frank, 2014; Gheza et al., 2019). Specifically, synchronized theta oscillations have been suggested to coordinate neural activity, whereby the pMFC works in concert with dorsolateral prefrontal areas to implement cognitive control to support adaptive behavioral adjustments following errors (see Fig. 1) (Narayanan et al., 2013; Ullsperger et al., 2014a).The PM related ERPs are proposed to reflect the phase-locked midfrontal theta activity (Makeig et al., 2002; Van Noordt et al., 2016). On the behavioral level multiple adaptations following an error can be observed (dependent on task, trial-timing, instructions and so forth; for a review, see Danielmeier and Ullsperger, 2011). For example, subjects can slow down in responses following an error (post-error slowing, PES), their accuracy can improve in post-error trials (post-error improvement in accuracy; PIA) or effects of response conflict can be less pronounced in trials following an error (post-error reduction in interference; PERI). There is growing literature linking the behavioral post-error adaptions to the neural error signal noted above (Debener et al., 2005; Fu et al., 2019).

The neural and behavioral indices of performance monitoring discussed above have been reliably studied in diverse human samples ranging from healthy to various clinical populations across the lifespan (Weinberg et al., 2015). Moreover, a growing body of research is linking stronger activity of the before mentioned ERP-complex associated with performance monitoring to better cognitive functioning (Hirsh and Inzlicht, 2010; Larson and Clayson, 2011; Miller et al., 2012). However, oversimplified interindividual links between ERP amplitudes and performance monitoring have been challenged in the past (see Fischer et al., 2016 and discussion for more information).

1.3. Motivation and goals of the current review

Starting back in 1999 Kopp and Rist (1999) were able to show a reduced ERN in patients suffering from paranoid schizophrenia while behavioral indices of performance monitoring were intact in this patient population. Ever since then a number of studies has addressed performance monitoring deficits in schizophrenia. Evidence from meta-analysis on EEG (Martin et al., 2018; Storchak et al., 2021) and functional neuroimaging (Minzenberg et al., 2009) correlates of performance monitoring in the wider spectrum of psychosis indicate that alterations in performance monitoring may be involved in schizophrenia. However, current reviews demonstrated inconclusive evidence for a relationship between disrupted error signals (e.g., blunted ERN) and post-error behavioral adaptations. Hence it is difficult to relate these findings to broader deficits in cognitive control and derive a functional link between disrupted error signals and behavioral adaptations in schizophrenia. In addition, inconsistent results regarding the Pe are reported (Martin et al., 2018; Storchak et al., 2021) which, may in part result from rather heterogeneous diagnosis included in this literature. Therefore, more comprehensive reviews on the literature *across* different performance monitoring matrixes (i.e., electrophysiological correlates complemented by their neuro-functional underpinnings and behavioral indices of performance monitoring like post error adjustments) but *within* clearly defined patients suffering from schizophrenia are needed to better understand the pattern of alterations associated with schizophrenia and link results to underlying functional mechanisms.

In the following sections, we will review recent research on behavioral and neural correlates of performance monitoring in patients with an established clinical diagnosis of schizophrenia (while excluding schizoaffective or other psychotic disorders and subclinical or at-risk populations). Studies focusing on psychiatric relevant abnormalities in reward processing are not in the scope of this review. A summary of the main findings and detailed information on the systematic literature search can be found in the corresponding supplementary sections. We will then discuss disrupted midfrontal theta activity as a possible neurobiological mechanism that underlies dysfunctions in PM and cognitive deficits in schizophrenia.

2. Biobehavioral correlates of performance monitoring in schizophrenia

2.1. Behavioral indices

In this section we review the evidence of general performance and behavioral indices of post-error adjustments (Danielmeier and Ullsperger, 2011) in performance monitoring tasks in schizophrenia.

2.1.1. General performance indices

In terms of general performance, the majority of studies report prolonged reaction times (RT) in schizophrenia (Alain et al., 2002; Bates et al., 2002; Becerril and Barch, 2013; Becerril et al., 2011; de la Asuncion et al., 2015; Foti et al., 2012; Houthoofd et al., 2013; Huddy

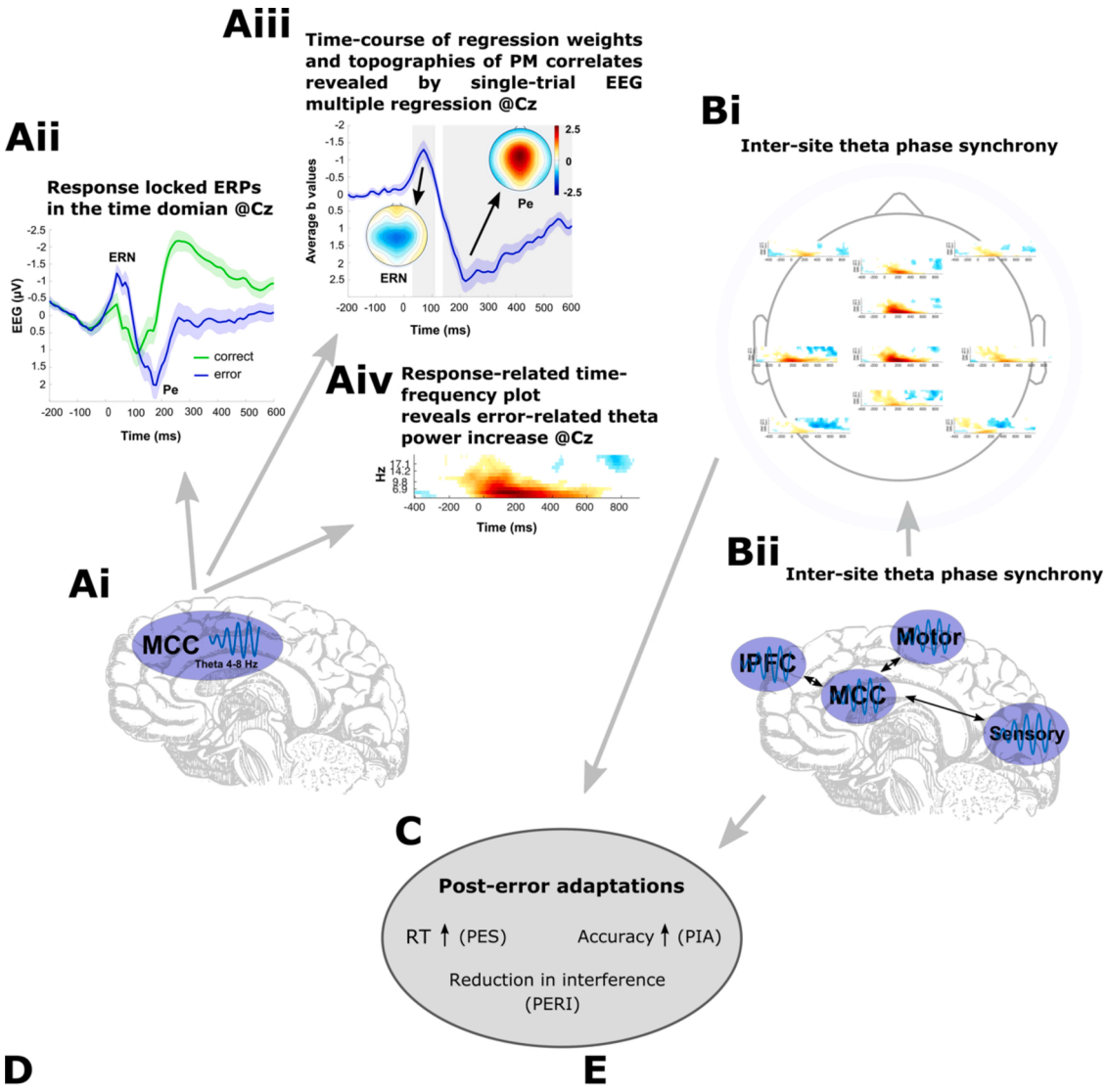

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Fig. 1. Error-related midfrontal theta activity and the implementation of post-error adaptations. **(Ai)** Theta-related readouts on the scalp are thought to be generated by theta oscillations in the MCC (van Noordt and Segalowitz, 2012). **(Aii)** Event-related potentials (ERPs) reflect theta-related activation in the time domain. The ERN and Pe are evoked by motor commission errors in simple speeded response tasks. They are thought to reflect phase-locked theta generated in the MCC (Ullsperger et al., 2014a, b). However, due to trial-averaging, ERPs do only reflect a small fraction of ongoing neural dynamics. **(Aiii)** Time-course of regression weights and their topographies of error-related EEG activity revealed by single-trial robust regression. Specifically, here we depict the regression weight time course of a response-locked error regressor. This analyses approach has the appealing benefit to provide richer information of trial-by-trial dynamics and independent contributions of different processes to the EEG time-course (Fischer et al., 2018; Fischer and Ullsperger, 2013; Ullsperger et al., 2014b). **(Aiv)** Here we employed multiple robust regression on time-frequency decomposed response-locked EEG. Shown is the time-frequency plot for the error regressor that reveals a common significant increase in theta power after error commission. Analyses in the time-frequency domain have the advantages to show richer spectral dynamics of event-related EEG activity, whereby the signal is not required to be phase-locked (Cavanagh and Frank, 2014). **(Bi)** Inter-site theta-phase synchrony at the scalp is thought to reflect the synchronization and communication of local activity across multiple brain regions **(Bii)**, including the lateral prefrontal cortex (lPFC), motor cortex, and sensory cortices. **(C)** Inter-site phase synchrony is proposed to reflect the communication of the need for control and the implementation of adjustments aimed at optimizing performance (e.g., attention reorientation in the lPFC; motor threshold adjustments in the motor cortex; boosting sensory gain in sensory cortices) (Cavanagh and Frank, 2014). Importantly, the coordination of higher oscillations in the alpha and gamma band also contribute to this optimization process (Gratton, 2018). **(D)** Summary of midfrontal theta-related dysfunctions and their relation to behavior adaptations and real word functioning in schizophrenia. **(E)** List of main implications derived from the current review. Data presented in **(Aii)**, **(Aiii)**, **(Aiv)**, and **(Bi)** are from a healthy sample who performed an interference and multi-rule target detection task (Kirschner et al., 2020).

et al., 2011; Kansal et al., 2014; Laurens et al., 2003; Llerena et al., 2016; Mathalon et al., 2002; Morris et al., 2008, 2011; Nordahl et al., 2001; Perez et al., 2012). The picture regarding general task performance is less clear. While several studies report underperformance in patients (Agam et al., 2014; Becerril et al., 2011; Charles et al., 2017; Donaldson et al., 2019; Houthoofd et al., 2013; Krawitz et al., 2011; Llerena et al., 2016; Nordahl et al., 2001; Perez et al., 2012), other studies show comparable task performance (Alain et al., 2002; Araki et al., 2013; Bates et al., 2009, 2004; de la Asuncion et al., 2015; Foti et al., 2012, 2013; Kansal et al., 2014; Laurens et al., 2003; Mathalon et al., 2002; Morris et al., 2011, 2006). Importantly, the proportion of overall errors was relatively low for patients and task manipulations (e.g., interference effects see Donaldson et al. (2019)) affected both patients and healthy controls. Moreover, the performance in these tasks seems to be fairly stable over time (Bates et al., 2004; Foti et al., 2016). Differences between groups appear to be task dependent. While patients diagnosed with schizophrenia are relatively unimpaired in their performance in simple reaction-time tasks (e.g., flanker tasks), there is a consistent performance deficit in tasks that required to hold task rule representations in working memory (Becerril et al., 2011) and during antisaccade tasks (Agam et al., 2014; Huddy et al., 2011; Polli et al., 2008, 2006; Roffman et al., 2011).

2.1.2. Post-error adjustments

One important behavioral aspect of performance monitoring are post-error adjustments (i.e., behavioral changes after error commission). As introduced above three types of behavioral-post-error adaptations have been proposed (Danielmeier and Ullsperger, 2011): post-error slowing (PES), post-error-reduction of interference (PERI), and post-error improvements in accuracy (PIA). In the studies examined in this review there appeared to be a focus on PES. A number of studies report comparable PES between groups (Araki et al., 2013; Bates et al., 2002, 2009; Laurens et al., 2003; Mathalon et al., 2002; Morris et al., 2006; Polli et al., 2006), but other studies indicating a reduced (Alain et al., 2002; Donaldson et al., 2019; Perez et al., 2012) or absent (Becerril et al., 2011) PES in schizophrenia. There might be several reasons that contribute to these mixed findings. For example, performance between groups was frequently not matched and the inter-trial-intervals fluctuated in a wide range. Given that both of these factors are suggested to influence PES (Danielmeier and Ullsperger, 2011) it is important to control for these methodological aspects to interpret differences in PES in patients vs. controls. Indeed, Castellar et al. (2012) matched the performance in a 4-choice RT task between patients diagnosed with schizophrenia and controls and found that PES in Schizophrenia depended on the inter-trial-interval (ITI). In particular, shorter ITI lead to longer PES in schizophrenia. These results fit well with the orientation account of PES, which states that PES is an orientation response to unexpected events (Danielmeier and Ullsperger, 2011; Notebaert et al., 2009) and increased distractibility in schizophrenia (Braff, 1993). In terms of other post-error adaptations, there is evidence of intact error corrections in patients from antisaccade tasks (Polli et al., 2008, 2006). Here, patients showed the same rate of antisaccade error self-correction as healthy controls.

2.2. EEG correlates

2.2.1. ERN and Pe – internal performance feedback

With respect to performance monitoring impairments during early error processing, the results of the studies reviewed here provide clear and consistent evidence of an ERN reduction across a broad set of tasks in those diagnosed with schizophrenia (see Supplementary Table 1). Moreover, blunted ERN amplitudes show impressive stability (Bates et al., 2004; Foti et al., 2016; Houthoofd et al., 2013). Early neural performance monitoring impairments were also found in unaffected siblings, supporting the hypothesis that this impairment is not a mere consequence of behavioral disturbance, and that it is a trait marker for susceptibility to schizophrenia or a potential endophenotype, rather than being a result of illness or medication (Simmonite et al., 2012). ERN deficits in schizophrenia are present even under conditions demonstrated to maximize the ERN amplitude (Morris et al., 2006). Regarding the CRN, there is evidence for increased amplitudes in some studies (Alain et al., 2002; Araki et al., 2013; Mathalon et al., 2002), which may suggest a general deficit in self-monitoring in schizophrenia (Olvet and Hajcak, 2008).

Interestingly, the mechanism by which conflict increases the ERN appears to be intact in schizophrenia, despite a general deficit in ERN amplitude in this population (Donaldson et al., 2019). Specifically, Donaldson et al. (2019) demonstrated that the probability of incongruent trials in a flanker task similarly affected ERN amplitudes in patients as well as in healthy controls. In addition, there is evidence that the ERN amplitude was similarly associated with self-correction and post error accuracies in schizophrenia and healthy controls (Morris et al., 2006). However, there is also evidence from a rather small sample showing that compared to healthy controls, no link between ERN amplitude and PES is found in schizophrenia (Alain et al., 2002). The small sample size ($n = 12$) of this study precludes generalizations of these findings.

Unlike the consistently reduced ERN, the Pe was reduced in schizophrenia in some (Donaldson et al., 2019; Foti et al., 2012, 2013; Kansal et al., 2014; Simmonite et al., 2012), but not all studies (Alain et al., 2002; Bates et al., 2004; Llerena et al., 2016; Morris et al., 2006). When having a closer look at the Pe null findings, these results can be explained by either a limited sample size (Alain et al., 2002), the applied signal filters (i.e., severe higher-frequency cutoffs between 1–2 Hz likely to attenuate some of the Pe activity (Bates et al., 2004; Morris et al., 2006), or different analysis strategies (i.e., temporal principal

component analysis (Llerena et al., 2016)). Given that Pe has been related to conscious error awareness and decision confidence (Boldt and Yeung, 2015; Endrass et al., 2007; Kirschner et al., 2020), these results may point towards an altered meta-cognitive performance monitoring in schizophrenia. Supporting this assumption, Charles et al. (2017) demonstrated, that ERN deficits in patients appear to be related to conscious top-down deficits. Specifically, they showed that, patients displayed decreased ERN and error awareness on trials where errors could be consciously perceived. This is further augmented by studies demonstrating metacognitive deficits in schizophrenia in other cognitive domains like metamemory (Rouy et al., 2021) and the often reported lack of awareness of their disorder that seems to be mediated by alteration of the right posterior insula (Klein et al., 2013).

Taken together, the ERN and Pe are promising measures of impaired error processing, with the ERN reduced in psychotic illness broadly and the Pe reduced specifically in schizophrenia (Foti et al., 2016). In addition, there is evidence that blunted ERN is related to negative symptoms and that patients with relatively intact ERN had less rehospitalization and better employment status (Foti et al., 2012, 2013). This validates the ERN as potential marker for cognitive deficits in schizophrenia. Importantly, differences in ERN and Pe remain, after controlling for behavioral measures like error rate or RT (Donaldson et al., 2019). Computational modeling suggests decreased representation of response values in schizophrenia may contribute to blunted error-related EEG components (Morris et al., 2011). Several factors suggest that ERN and - to some extent - the Pe may be useful endophenotypes for schizophrenia. For example, there is evidence, that unaffected siblings also show ERN reductions, indicating that smaller ERN is related to a genetic risk for developing this illness (Simmonite et al., 2012). Moreover, ERN and Pe reductions are fairly state-independent and longitudinally stable (Foti et al., 2016). In addition, individuals at risk of developing schizophrenia[1] also show reductions in the ERN amplitudes (Perez et al., 2012). Another intriguing aspect of these performance monitoring abnormalities in schizophrenia is, that they relate to functional outcome (Foti et al., 2012, 2013). In a recent study, Foti et al. (2020) showed that both blunted ERN and Pe amplitudes were related to negative symptoms and poor real-world functioning in schizophrenia and other psychotic disorders. This link was mediated by poor executive functioning assessed in separate tasks.

2.3. FRN – external performance feedback

While research has consistently shown that patients with schizophrenia show impairments in internal performance monitoring, the relatively few findings from studies included in this review suggest that neural correlates of external feedback may be intact in simple response feedback tasks like time estimation tasks (Llerena et al., 2016; Morris et al., 2011). Interestingly, in acute and non-medicated state of schizophrenia, there are deficits in neural feedback processing (reflected in blunted FRN) that are normalized with treatment (Houthoofd et al., 2013). In addition, patients in the early course of schizophrenia demonstrated impairments to adaptively use negative feedback in a simple rule switching task (Huddy et al., 2011). In contrast, feedback processing in schizophrenia appears to be abnormal during reward processing in probabilistic learning tasks (Morris et al., 2008). These effects have been related to dysfunctional phasic striatal dopamine signalling (Whitton et al., 2015). However, dysfunctional reward processing in schizophrenia fall beyond the scope and space of the present review (see for example Whitton et al. (2015) for discussions on this topic).

Taken together, these results suggest that, impaired internal error processing may be an important trait-like marker in schizophrenia, while deficits in feedback processing appears to have a state character (i.e., they appear in acute sates of schizophrenia but normalise with treatment) and appear to be task specific.

2.4. Neuroimaging studies – what are the neural underpinnings of the EEG effects?

Structural neuroimaging studies suggest widespread brain abnormalities in schizophrenia. Early in the course of the illness, volume decreases are found in the bilateral insula and the mid-cingulate cortex (MCC), as well as the hippocampus, thalamus and left uncus and amygdala (Crossley et al., 2009). Later during disease progression, cortical volume reductions become widespread and are correlated with cognitive dysfunction (Ellison-Wright et al., 2008; Kahn et al., 2015; Kubota et al., 2015; van Haren et al., 2011). Results from functional neuroimaging studies suggest, that the broad impairment in cognitive functioning in schizophrenia is reflected in neural system-level alterations (Kahn et al., 2015). In the following we review results of dysfunctions in the performance monitoring network in schizophrenia.

Although exact anatomical regions associated with performance monitoring reported varies across studies due to different naming conventions, the majority of studies reviewed here report a blunted error-related activity in the posterior medial frontal cortex (pMFC, Ridderinkhof et al., 2004) related to schizophrenia (Becerril et al., 2011; Krawitz et al., 2011; Laurens et al., 2003; Polli et al., 2008; Stern et al., 2009; Voegler et al., 2016; but see Agam et al., 2014). Voegler et al. (2016) demonstrated, that this reduced neural error signal is independent of error frequency and is also associated with reduced functional connectivity between the right anterior insula and regions in the inferior frontal gyrus and temporoparietal junction. These results fit well with research showing reduced response-related mid-line theta oscillations in schizophrenia (Bates et al., 2009; Boudewyn and Carter, 2018; Chidharom et al., 2021; Reinhart et al., 2015a; Ryman et al., 2018), which may help explain the decreased recruitment of brain areas involved in performance monitoring. Specifically, in the normative literature frontal midline theta has been suggested as a biophysical mechanism by which neurons communicate the need for and subsequently implementation of cognitive control processes across the brain (Cavanagh and Frank, 2014). The biobehavioral results in schizophrenia reviewed above suggest that this control process appears to be decreased when patients have to rely on internal feedback processing. In contrast, when information about errors and conflicts are explicitly provided by the task structure, error-related activity in the pMFC seems to be relatively preserved (Becerril and Barch, 2013). This imaging study is mirroring the EEG results for external feedback processing in schizophrenia reviewed above. In unmedicated patients diagnosed with paranoid schizophrenia, one study reported a trend towards increased error-related metabolic activity in the pMFC (Nordahl et al., 2001). This may suggest that error sensitivity in this region is preserved to some extent in this specific patient group.

3. Discussion and outlook

In this review, we investigated disrupted performance monitoring in schizophrenia. We found that recent research on behavioral and neural correlates of performance monitoring in schizophrenia show a consistent impairment of early (ERN) and late (Pe) internal error processing. These deficits are linked to aberrant functioning of the pMFC and the wider performance monitoring network during error processing. Form a mechanistic perspective this disrupted internal error monitoring may be related to decreased midfrontal theta activity. On the other hand, external performance feedback processing in simple response feedback tasks is relatively preserved in schizophrenia. This conclusion is broadly validated by more formal metanalyses on EEG (Martin et al., 2018; Storchak et al., 2021) and functional neuroimaging (Minzenberg et al., 2009) correlates of performance monitoring in the wider spectrum of

[1] These patients met criteria for at least one Criteria of Prodromal Syndromes (COPS; Miller et al., 2003).

psychosis. Martin et al. (2018) discuss their findings of a reduced ERN in a wider range of patients with psychotic symptoms in terms of structural and functional abnormalities in the anterior cingulate cortex (ACC). Moreover, the authors suggest that adaptive error processing needs coordinated activity throughout a network of different brain regions to optimize behavior after errors and that blunted ERN may be an index of the failure to initiate cognitive control in schizophrenia (see Minzenberg et al., 2009 for a similar discussion). Storchak et al. (2021) report a reduced ERN or a reduced discriminability between positive and negative action outcomes in schizophrenia and schizoaffective disorders because of a more global deficit in predictive processes (are outcomes better or worse than expected) in patients suffering from schizophrenia. They claim that especially early processes in performance monitoring (i.e., the ERN) are subject to pathological changes and are associated with positive symptoms while later processes (i.e., the Pe) seem to be intact. Initially, the latter finding seem to point towards preserved error awareness in schizophrenia. However, a closer evaluation of these findings indicates, that it may not be that straightforward. Null findings regarding the Pe may be better explained by methodological differences between the studies. Future work is needed to answer the question, whether deficits in metacognitive functions, such as error awareness, contribute to blunted ERN and Pe amplitudes in schizophrenia.

A major goal of this narrative review was to investigate whether disrupted error processing leads to impaired behavioral adaptations in schizophrenia and to related a plausible neurobiological mechanism to this pattern of results. Impaired midfrontal theta oscillations have recently been suggested as an fundamental cognitive subprocess that is affected in psychiatric disorders and relates to cognitive deficits, such as reduced behavioral adaptations (McLoughlin et al., 2021). The inconsistent association between impaired internal error processing and behavioral adaptations demonstrated in the current review suggest, that it is too early to clearly link neural PM indices to behavior in schizophrenia. By integrating our biobehavioral findings into the emerging research on disrupted theta-related dynamics as an index of cognitive control deficits in schizophrenia, we argue, that finer-grained trial-by-trial analyses are needed to parse the current pattern of results into finer levels of detail.

3.1. Abnormal neural oscillations in schizophrenia may best explain reduced ERP correlates of internal error processing

Evidence from anatomical and electrophysiological studies show that abnormal neural oscillations are central to cognitive deficits in schizophrenia. Specifically, pre-frontal cortex-related dysfunctional neural activation and synchronization in the gamma and theta band have been related to cognitive deficits in schizophrenia (Senkowski and Gallinat, 2015; Uhlhaas and Singer, 2010). In healthy individuals, gamma activity (i.e., oscillations $>$ 30 Hz) facilitates the synchronization of local cortical networks (Womelsdorf et al., 2007). Lower frequencies like theta are thought to modulate the power in the gamma spectrum (Canolty et al., 2006) and to coordinate neural activity over longer cortical distances (von Stein et al., 2000). As noted above and illustrated in Fig. 1, midfrontal theta activation has been suggested as an index of the recruitment of cognitive control (Cavanagh and Frank, 2014) and is thought to be generated in the MCC (van Noordt and Segalowitz, 2012). Research showed that disrupted midfrontal theta might reflect the failure to initiate cognitive control in speeded reaction time tasks in schizophrenia (Boudewyn and Carter, 2018; Chidharom et al., 2021; Reinhart et al., 2015b; Ryman et al., 2018). Specifically, disrupted phase coherence across trials may underly cognitive deficits on schizophrenia (Reinhart et al., 2015a). In addition, there is also evidence of impaired theta-gamma coupling during cognitive functioning in schizophrenia (Barr et al., 2017) indicating an involvement of impaired coordination of theta and gamma activation in cognitive deficits in this group. These abnormalities are likely caused by anatomical deficits (e.g., reduced synaptic connectivity) and abnormalities in neurotransmitter systems (in particular GABA-ergic interneurons) that have been found in patients with schizophrenia (for a review on the neuobiology of abnormal oscillations in schizophrina see Uhlhaas and Singer, 2010). In the time domain, midfrontal theta activity has been strongly related to the ERN and the FRN (Van Noordt et al., 2016). These theta-related ERPs are thought to reflect either phase resetting of theta oscillations after a stimulus (FRN) or response (ERN) or evoked theta due to the event itself (Makeig et al., 2002). Hence, the reliable blunted ERN in schizophrenia can be directly related to reduced midfrontal theta in the time domain (see Figure Aii and Aiii).

To date, electrophysiological investigations of performance monitoring in psychopathology have predominantly used grand mean ERP data (i.e., trial-averaging in the time domain). This work has revealed that ERN alterations may be a promising endophenotype across disorders like schizophrenia (see also 2.2.1), substance use disorder, and OCD (Riesel, 2019). Such endophenotypes have the potential to inform prevention, refine classification criteria, link basic empirical neuroscience and clinical praxis, and help to better target and evaluate treatments (Riesel, 2019). For example, studies showed that combining multiple neural and behavioural metrics of error processing help to better classify and predict mental disorders (Cavanagh et al., 2017; Meyer et al., 2018). The ERN may lend itself particular well as a easy to assess marker of cognitive deficits in schizophrenia and across psychiatric illness as it is robustly measured within only a few trials (e.g., Fischer et al., 2017 demonstrated that ERN reaches a high reliability within subjects with a trial number of 15) and because EEG is routinely integrated into the clinical practice (Cavanagh, 2019). However, trial-averaging in the time domain leads to substantial loss of information and precludes the analyses of trial-to-trial associations between neural signals and behavioral adjustments (Ullsperger et al., 2014b). Moreover, the focus on a single aspect of midfrontal theta (e.g., the ERN) strongly limits investigations of its full functional role in psychiatric conditions like schizophrenia (McLoughlin et al., 2021). In particular, time-frequency analyses enable investigations of power modulations and phase relationships related to cognitive control processes and directly relate to behavioral adjustments (see Fig. 1B and C).

3.2. What's next?

Utilizing single-trial analyses in the time and time-frequency domain will help to investigate the role of midfrontal theta signals in transient and ongoing deficits in cognitive control processes in schizophrenia (see also Figure Aiii and Aiv). Indeed, a recent study demonstrated that midfrontal theta activation was specifically disrupted in patients during periods of high RT variability and increased errors (Chidharom et al., 2021). This suggests, that deficits in theta signals in schizophrenia might be related to attentional fluctuations and should not only be evaluated on an inter-individual basis, but also on an intra-individual level. These intra-individual fluctuations during task performances might also contribute to the inconsistent relationship between blunted theta signals in the time domain (i.e., a blunted ERN) and post-error adaptation found in this review. As for the neural data, grand mean averaging of behavioral data may have precluded the evaluation of trial-by-trial dynamics in post-error adaptions. This issue has been repeatedly put forward in the literature (Derrfuss et al., 2021; Dutilh et al., 2012). Moreover, we know from the normative literature that for the error signal to be adaptive, the inter-trial-interval (ITI) has to be long enough (Jentzsch and Dudschig, 2009; Wessel, 2018). Mass-univariate multiple robust regression analysis across single trial EEG data and behavior (Fischer et al., 2016; Fischer and Ullsperger, 2013; Ullsperger et al., 2014b) will help to better understand if, how and under which conditions reduced theta signals are related to adjustments of behavioral responses.

There is evidence in healthy individuals, that in-phase theta stimulation over the medial frontal cortex (MFC) and the right lateral prefrontal cortex (lPFC) using transcranial direct current stimulation (tDCS) can improve adaptive behaviour lasting longer than 40 min (Reinhart,

2017). Using a similar design, it was possible to normalize synchrony over MFC and lPFC following errors in patients with schizophrenia, which also resulted in a normalization of their PES (Reinhart et al., 2015b) and better learning (Reinhart et al., 2015a). These results highlight the involvement of midfrontal theta activity in cognitive function and its potential as a novel treatment target. Further work is need to evaluate the potential of theta modulation as a therapeutic tool in clinical setting and its relation to cognitive improvements outside the laboratory.

Besides studying the dynamic involvement of midfrontal theta signals in the process of cognitive deficits, future work may be complemented by representational similarity analysis (RSA) to better understand cognitive deficits in terms of maladaptive cognitive control representations (see Freund et al., 2021 for a recent review on the usefulness of RSA within several recent RSA studies on cognitive control).

3.3. Are effects driven by medication?

An important question is to what extent disrupted theta activity seen in patients with schizophrenia are affected by antipsychotic medication. Indeed, the majority of studies reviewed here are conducted with patients who were taking antipsychotic medications at the time of the study. In contrast, there is some evidence that abnormal neural oscillations are present in schizophrenia regardless of medication-status (Gallinat et al., 2004; Spencer et al., 2008), suggesting that disrupted oscillations are present in schizophrenia regardless of medication status. However, it is possible, that medication may interact with task performance and brain activity. Critically, most participants are taking different antipsychotic medications at different doses. This may preclude post-hoc analyses examining the role of medication with sufficient power. Here, dose equivalents for antipsychotics (Leucht et al., 2016) may server as parameter that controls for such a confound. More research is needed to address this important issue. One way of directly investigate the effect of medication does on theta activity is to include dose equivalents as a 2nd level predictor in the regression analyses described above.

4. Conclusions

Cognitive deficits are central to the pathology of many mental disorders, and mounting evidence suggests that neural and behavioural metrics of error processing may be biobehavioural markers or even endophenotypes of such deficits. Here, we reviewed alterations in performance monitoring in schizophrenia. We found that performance monitoring alterations in schizophrenia are specific to early (ERN) and late (Pe) internal error processing, while external performance feedback processing in simple response feedback tasks is relatively preserved. On a functional level, these performance monitoring deficits may be considered as an aspect of disrupted midfrontal theta (i.e., an index of the recruitment of cognitive control) in patients with schizophrenia. While theta-related ERPs (the ERN) may be an easy to assess marker of cognitive deficits in schizophrenia, further work investigating the trial-by-trial dynamics of theta in both the time and time-frequency domain is needed to parse cognitive deficits in schizophrenia into finer levels of detail.

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Appendix A. Supplementary data

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