Event-related potentials and cognition in Parkinson's disease: An integrative review

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Abstract

Cognitive impairment is a common non-motor symptom of Parkinson's disease (PD), but the nature of cognitive changes varies considerably between individuals. According to the dual-syndrome hypothesis, one cluster of patients is characterized by deficits in executive function that may be related to fronto-striatal dysfunction. Other patients primarily show non-frontal cognitive impairments that progress rapidly to PD dementia (PDD). We provide a comprehensive review of event-related potential (ERP) studies to identify ERP measures substantiating the heterogeneity of cognitive impairment in PD. Our review revealed evidence for P3b and mismatch-negativity alterations in PDD, but not in non-demented PD, indicating that alterations of these ERPs constitute electrophysiological markers for PDD. In contrast, ERP correlates of executive functions, such as NoGo-P3, N2, and error(-related) negativity (N_e/ERN), appear to be attenuated in non-demented PD patients in a dopamine-dependent manner. Hence, ERP measures confirm and yield distinct electrophysiological markers for the heterogeneity of cognitive impairment in PD. We discuss limitations and open questions of the ERP approach and provide directions and predictions for future ERP research.

Keywords: Parkinson's disease, Cognition, Dementia, Executive function, Basal ganglia, Dopamine, Event-related potentials (ERPs), P3, P3a, P3b, MMN, NoGo-P3, N2, N_e/ERN

1   Introduction

Event-related potentials (ERPs) represent neural activities that are gained from the scalp-recorded electroencephalogram (EEG) (Luck, 2014). ERPs are usually calculated by averaging EEG activity that is time-locked to the occurrence of an observable event, e.g., a sensory stimulus (i.e., *stimulus-locked ERP*), or the onset of a motor reaction (i.e., *response-locked ERP*). ERPs are thought to reflect the summation of postsynaptic potentials of large ensembles of synchronously active pyramidal neurons in the cerebral cortex (Woodman, 2010). Distinct waveforms of the ERP are characterized by their polarity, scalp distribution, latency, and by their sensitivity to particular experimental manipulations. These fluctuations can be conceived of as neural correlates of information processing (Duncan et al., 2009). ERP measurements have an excellent temporal resolution that allows for the investigation of cognitive processes that occur in rapid succession. In addition, ERPs also provide a non-invasive tool also for the assessment of disease-related changes in brain functioning (e.g., Duncan et al., 2009; Verleger, 2003).

ERP latencies are related to the time course of cognitive processes, such as the evaluation of a stimulus and the selection and preparation of an appropriate response. ERP amplitudes are considered to indicate the extent to which neural resources are allocated to these processes. The measurement of ERP latencies and/or amplitudes can thus provide valuable diagnostic information about cognitive and neural functions and dysfunctions, over and above behavioral performance measures (Duncan et al., 2009).

The present work presents an overview of the literature concerning ERP correlates of cognitive dysfunction and decline in idiopathic Parkinson's disease (PD). In the following sections, we will briefly review the cognitive impairment in PD, and we will introduce the most common and important ERPs related to cognitive functions in general and executive control in particular. Our focus is on four major cognitive ERP waveforms: mismatch negativity (MMN),

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P3, N2, and error(-related) negativity (N_e/ERN). All these ERPs have been well characterized in terms of their eliciting events, and they have been related to quite specific cognitive processes and/or functional neural networks.

1.1   Cognition in Parkinson's disease

PD is one of the most common neurodegenerative disorders, with an incidence of 8–18 per 100,000 person-years (de Lau and Breteler, 2006). The prime characteristic of PD at the time of clinical diagnosis is degeneration of dopaminergic neurons in the substantia nigra pars compacta, which results in a depletion of dopamine in the basal ganglia. The cardinal motor symptoms of PD are bradykinesia, resting tremor, rigidity, and postural instability. However, PD is a multisystem neurodegenerative disorder. Namely, the intracerebral formation of Lewy bodies begins at defined anatomical brain sites and advances in a topographically predictable sequence. During pre-clinical stages, pathology is confined to the medulla oblongata/pontine tegmentum and olfactory bulb/anterior olfactory nucleus. In early symptomatic stages, the substantia nigra becomes the focus of pathological changes, whereas in the end-stages of the disease, the Lewy-related pathological processes enter the neocortex, and the disease manifests itself in all of its clinical dimensions (Braak and Del Tredici, 2008; Hawkes et al., 2010).

In addition to the motor symptoms, the course of neuropathological alterations in PD is associated with specific cognitive dysfunction and cognitive decline. In early clinical stages, cognitive dysfunction may be mainly attributed to the disruption of dopaminergic signaling in fronto-striatal loops, whereas the progression of the disease to its end stages may lead to Parkinson's disease dementia (PDD) in up to 90% of the patients with PD (Gratwicke et al., 2015). Furthermore, it appears that the patterns of cognitive impairment in PD are heterogeneous in nature (Miller et al., 2013), which has led to the proposition of two clusters of PD patients. According to this 'dual-syndrome hypothesis' (Kehagia et al., 2013; Robbins and Cools, 2014),

one cluster is formed by non-demented PD patients with mild cognitive impairment who show

deficits in tests of planning, task switching, inhibition, conflict processing, phonemic fluency,

working memory, and feedback-based learning. This pattern of deficits in executive function

likely reflects fronto-striatal dysfunction (Dirnberger and Jahanshahi, 2013), and has been shown

to be partly reversible by dopaminergic medication (Kehagia et al., 2013). In contrast, the second

cluster of PD patients has been described to show early deficits in non-frontal cognitive functions

(such as visuospatial abilities) that are predictive of rapid progression to dementia (PDD)

(Robbins and Cools, 2014; Williams-Gray et al., 2009). PDD involves a wide range of cognitive

and psychiatric symptoms that have been attributed to dysfunction in temporal and parietal areas

of the cortex (Gratwicke et al., 2015; Kehagia et al., 2013). These cognitive symptoms in PDD

(assessed, for instance, using the Mini-Mental State Examination, MMSE, Folstein et al., 1975)

are apparently unresponsive to dopamine substitution, but may instead benefit from cholinergic

treatment (Emre et al., 2004; Robbins and Cools, 2014).

Apart from the discussion of dopaminergic/cholinergic medication for dementia in PD, it

is important to note that the effect of dopaminergic medication on cognition is variable – even in

early (non-demented) PD patients. While in these patients dopaminergic medication can improve

cognitive functions mediated by the motor or associative fronto-striatal circuits, it can lead to

'overdosing' and impairment of performance on cognitive tasks that rely on the limbic or

orbitofrontal circuits, which are not dopamine-depleted in early stages of the disease (Cools et al.,

2001; Cools, 2006; Gotham et al., 1988; Jahanshahi et al., 2010; Swainson et al., 2006). This

issue will be discussed in more detail in Section 4.4.

1.2   Cognitive ERPs

In the next two paragraphs, we will introduce classical ERPs that might qualify as

indicators of cognitive decline in PDD, as well as ERP correlates of executive processes that have

been used to examine the specific cognitive sequelae of fronto-striatal dysfunction in non-demented PD patients.

1.2.1 Classical cognitive ERPs

The P3b, first described by Sutton et al. (1965) and often also referred to as P300, is perhaps the most-studied ERP component, partly due to its relatively large amplitude and facile elicitation in experimental contexts (for reviews, see Kok, 2001; Polich, 2007). It emerges as a positivity with a parietal scalp distribution and is possibly related to noradrenergic signaling from the locus coeruleus (Nieuwenhuis et al., 2005). Timing of this ERP may range widely, from 250 ms and extending to up to 1000 ms. The P3b is commonly assessed using the 'oddball' paradigm, in which a random sequence of stimuli (of either visual, auditory or somatosensory modality) is presented (Fig. 1). Participants are required to mentally count or to press a button in response to rare target events ('oddballs') and hence to discriminate them from frequent standard events. In this two-stimulus oddball paradigm, stimuli belonging to the target category elicit the P3b, and P3b amplitudes increase with decreasing target category probability (Kolossa et al., 2013; Ritter and Vaughan, 1969). This inverse relation between the probability of the target category and P3b amplitude implies that P3b is elicited only after the stimulus has been evaluated as belonging to the frequent or infrequent category. Hence, P3b peak latency is commonly assumed to co-vary with the duration of stimulus evaluation. This relationship between P3b latency and stimulus evaluation time is further supported by the observation that P3b latency increases when the categorization of a stimulus as belonging to the target or standard category becomes more difficult (Kutas et al., 1977; Luck, 2014). In contrast, P3b latency appears to be relatively insensitive to increased demands for response selection (McCarthy and Donchin, 1981). Given the link between P3b peak latency and the duration of stimulus evaluation, P3b recordings can be used to decompose the variance in the speed of behavioral responses into an early portion

associated with stimulus evaluation and a late portion associated with post-perceptual processing. In addition, the amplitude of the P3b has been proposed to reflect the amount of attentional resources allocated to the target stimulus (Johnson, 1988).

If task-irrelevant novel and/or salient stimuli are added to the oddball task (i.e., three-stimulus oddball; Fig. 1), these deviant events also elicit a positive-going ERP waveform that has been labeled P3a (usually elicited by salient deviants; Squires et al., 1975) or novelty P3 (usually elicited by novel deviants; Friedman et al., 2001). As P3a and novelty P3 are commonly regarded as variants of the same ERP waveform (Polich, 2007; Spencer et al., 2001), we will collectively refer to both waveforms as P3a in the remainder of this review. The P3a can be distinguished from the P3b on the basis of earlier peak latency and a scalp distribution with a fronto-central maximum, relative to the more parietally distributed P3b maximum (Polich, 2007). The relation between P3a and P3b has not been fully clarified and remains an issue of theoretical debate. The P3a is often portrayed in the context of distraction through task-irrelevant events (Escera and Corral, 2007); however, the processing of salience and/or novelty may constitute an important alerting (or orienting) response of the brain to surprising events (Barceló et al., 2002; Kopp and Lange, 2013; Lange et al., 2015; Seer et al., 2016). EEG source modeling of scalp-recorded ERPs, intracranial investigation, studies with patients with focal brain lesions, and combined ERP/functional neuroimaging (fMRI) studies converge in suggesting that the main regions consistently attributed to generating the scalp-recorded P3b include the temporal-parietal junction and the medial temporal lobes, whereas generation of the P3a has been attributed to the prefrontal cortex (Polich, 2007; Volpe et al., 2007; Wronka et al., 2012).

The MMN (Näätänen et al., 1978; for reviews, see Näätänen and Winkler, 1999; Näätänen et al., 2007) is elicited by changes in auditory stimulation, and MMN amplitudes are related to the discriminability of these changes. The MMN is typically seen as a fronto-central

negativity, occurring in the latency range around 100–250 ms. It is generated from the auditory cortices bilaterally, but there may also be a contribution from the right lateral prefrontal cortex (Giard et al., 1990). The MMN is thought to reflect an automatic process that detects differences between an incoming stimulus and the sensory memory trace of immediately preceding stimuli (Näätänen et al., 2007).

1.2.2 Cognitive ERP correlates of executive control

One of the standard tasks to examine inhibitory control is the Go/NoGo task, in which participants are asked to respond to some stimuli and to refrain from responding to other stimuli (Fig. 1). ERPs measured in Go/NoGo tasks consist of a negative deflection (NoGo-N2) and a subsequent positivity (NoGo-P3) in NoGo-trials as compared to Go-trials (Falkenstein et al., 1995; Karlin et al., 1970). Both ERP waveforms show fronto-central scalp topography.

The NoGo-P3 has been related to neural processes for inhibition by many researchers (e.g., Roberts et al., 1994). However, the NoGo-P3 could simply reflect a separate inhibition-monitoring process (Bruin et al., 2001; Huster et al., 2013; Roche et al., 2005). Accordingly, the NoGo-P3 has been associated with the efficiency of inhibitory control and with the evaluation of the inhibition process (Liotti et al., 2005; Schmajuk et al., 2006; see also Kopp et al., 1996a). The network underlying NoGo-P3 generation shows a broad distribution of sources including medial prefrontal and pre-central sources and associations with pre-supplementary motor area (SMA), temporo-parietal regions, the insulae as well as parts of the basal ganglia (Huster et al., 2013).

The NoGo-N2 amplitude is smaller and NoGo-N2 latency is delayed in participants with higher error (false alarm) rates compared to participants with lower error rates (Falkenstein et al., 1999), supporting the view that the NoGo-N2 is related to inhibitory processing (Kopp et al., 1996a). The view that the NoGo-N2 reflects cognitive processes for inhibition was challenged by Nieuwenhuis et al. (2003) and Donkers and van Boxtel (2004), who suggested that the NoGo-N2

reflects response conflict rather than inhibitory control. This 'response conflict' view is consistent with the fact that simultaneous activation of competing response tendencies – as it occurs in conflict (or interference) tasks (such as the Eriksen flanker task, Eriksen and Eriksen, 1974; see Fig. 1) – is associated with enhanced fronto-central (conflict-)N2 amplitudes. Thus, both the NoGo-N2 (Kopp et al., 1996a) and the conflict-N2 elicited in interference tasks (Kopp et al., 1996b) have been claimed to indicate the resolution of response conflict by executive control processes (Folstein and Van Petten, 2008). EEG source modeling (Bekker et al., 2005; Bokura et al., 2001) and combined ERP/fMRI (Mathalon et al., 2003) studies suggest that the NoGo-N2 and conflict-N2 reflect activity in medial and lateral prefrontal cortices. The medial source seems to be located in the mid-cingulate cortex (Huster et al., 2013), whereas the lateral source has been attributed to the right (Lavric et al., 2004) and the left inferior prefrontal cortex (Huster et al., 2010). Note that the available data are still insufficient to unambiguously relate NoGo-N2, conflict-N2, and NoGo-P3 ERP measures to specific executive functions (Huster et al., 2013).

Incorrect responses in various choice-response tasks are typically followed by a fronto-centrally distributed negative deflection that has been termed 'error negativity' (N_e; Falkenstein et al., 1991) or 'error-related negativity' (ERN; Gehring et al., 1993). It starts around the time of an overt erroneous response and peaks around 50–100 ms later. The N_e/ERN has thus been regarded as a correlate of performance monitoring, and several models have sought to explain its functional significance (Bernstein et al., 1995; Botvinick et al., 2001; Holroyd and Coles, 2002; for review and discussion, see Ullsperger et al., 2014b). Specifically, the reinforcement learning model of the N_e/ERN (Holroyd and Coles, 2002) views the N_e/ERN as neural activity related to the processing of a prediction error which is conveyed by midbrain dopamine neurons and broadcasted to prefrontal cortices. Accordingly, the N_e/ERN is considered to be generated in the

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posterior medial prefrontal cortex (mainly the anterior mid-cingulate cortex; Ullsperger et al., 2014a).

1.3   The present review

In the following, we comprehensively review the literature on the ERP correlates of cognitive dysfunction in PD. Our review is based on an exhaustive literature search using ISI Web of Science, PubMed, and Google Scholar, conducted in late 2014/early 2015 and updated in early 2016. To be included in this review, studies were required to report at least one ERP measure recorded from at least two patients with PD (i.e., single-case studies were not considered). Studies focusing on movement-related potentials in PD are reviewed by us in a related article (Georgiev et al., 2016). A small number of studies were published after we had updated our literature review (i.e., during the review and revision process), and these studies (Garrido-Vásquez et al., 2016; Kaufman et al., 2016; Tang et al., 2016) were not included in the systematic overviews presented below. From the review, it becomes evident that two major lines of cognitive ERP research in PD have been pursued over the last three decades. On the one hand, clinically-oriented research has focused on recording classical ERPs elicited in simple discrimination tasks. Specifically, there is a long-standing debate as to whether P3b latency might qualify as an electrophysiological biomarker for PD. Here, we provide a quantitative overview of P3b studies in PD which reveals that the prolongation of the P3b latency is related to the presence of dementia in PD rather than to PD itself. On the other hand, theory-driven research has investigated a broader variety of ERPs as candidate biomarkers of cognitive dysfunction in PD. These studies used diverse tasks to identify the neural substrates of PD-specific cognitive alterations, most notably though not exclusively, in the domain of executive functioning. ERP research in this area has revealed particularly intriguing insights with regard to attentional orienting (P3a), conflict processing (N2), and performance monitoring (N_e/ERN) in PD. In sum,

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based on the evidence reviewed, we will establish that the clinically-oriented research on classical cognitive ERPs and the experimentally-oriented analyses of 'executive ERPs' complement each other in revealing the multifaceted nature of the neural substrates of cognitive deficits in PD (see above).

2 P3b: allocation of attentional resources and stimulus evaluation duration

The cognitive ERP most frequently studied in patients suffering from PD is the P3b. The P3b peak latency has been considered a promising tool to quantify cognitive impairments (particularly cognitive slowing) associated with PD (Hansch et al., 1982). The P3b latency can be quantified in the absence of any overt response (e.g., by instructing the participant to silently count the target stimuli). Hence, in contrast to response time measures, P3b latency may be a good measure for the efficiency of cognitive processing in PD which is not confounded by the patients' motor impairments and can be measured even in patients with severe symptoms. Building on this premise, dozens of research groups have recorded the oddball P3b in PD patients to examine whether patients differ from healthy controls with regard to the speed of stimulus evaluation, as indicated by P3b latency, or with regard to the allocation of attention, as indicated by P3b amplitude. Further issues related to P3b measures are whether they can help to discriminate PD patients with and without dementia, and whether P3b assessment can contribute to the differential diagnosis of idiopathic PD from other types of parkinsonism. How far have we come with regard to answering these questions?

We have identified 65 studies that present P3b data from 74 samples of PD patients (Table 1). All of these studies applied the oddball paradigm and compared at least one P3b measure (latency or amplitude) between the patient group and an age-matched group of healthy controls. In 54 studies that quantified and compared P3b amplitudes, PD patients' amplitude measures were decreased in ten (19%), increased in five (9%), and indistinguishable from

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waveforms recorded in healthy controls in 39 (72%) samples, a pattern that might be best explained by chance variation.

P3b latency on the other hand was significantly prolonged in 39 (or 53%) of the samples, with only one study reporting shorter P3b latencies in PD patients than in controls. While such a large proportion of significant results can certainly not be attributed to error variance, it also highlights that there is no reliable pattern of P3b prolongation in PD. Basically, two alternative explanations might account for this observation: either the magnitude of the group difference between PD patients and healthy controls is not large enough, or the group difference is substantially influenced by a moderating factor. If the former is the case, studies involving a large sample size should be more likely to detect significant P3b latency differences. However, large-sample studies (as defined by a median split over N; the median number of participants was $N = 38$) did not generate a significantly larger number of significant results than small-sample studies (large N: 58%, small N: 49%; $\chi^2(1, n = 73) = 0.69$, $p = 0.41$). To address the second possibility, we tested whether the likelihood of finding significantly prolonged P3b latencies in PD patients depends on a number of sample characteristics (medication status [on vs. off dopamine replacement therapy vs. non-selected samples], age, disease duration, Hoehn & Yahr stage [HY], dementia status [diagnosis of dementia vs. no diagnosis of dementia vs. non-selected samples]), or on task settings of the oddball paradigm (two-stimulus vs. three-stimulus oddball, modality, target probability, response mode). For this purpose, continuous measures were transformed into binary variables by median split (median HY: 2.33; median age: 64.1 years; median disease duration: 5.4 years; median target probability: 0.20). As displayed in Fig. 2, the likelihood of finding significant P3b prolongations in PD was not affected by any of the factors (all $\chi^2 < 2.46$, all $p > 0.11$) with the exception of the presence or absence of a diagnosis of dementia in the PD sample ($\chi^2(1, n = 72) = 11.74$, $p = 0.001$) and HY stage ($\chi^2(1, n = 54) = 4.75$, $p = 0.03$). When

included in a logistic regression model ($R^2 = 0.27$), only dementia status (Exp(B) = 6.63, 95% CI = [1.54– 28.44], Wald(1) = 6.47, $p = 0.01$), but not HY (Exp(B) = 2.31, 95% CI = [0.68–7.84], Wald(1) = 1.79, $p = 0.18$) emerged as a significant predictor of the prolongation of P3b latency. When demented PD patients were excluded from consideration, only 19 of 50 studies (38%) yielded significant P3b latency differences. However, 10 out of 14 studies on non-selected samples and all of the eight studies on samples that only included demented PD patients demonstrated significantly increased P3b latencies in these patients in comparison to healthy controls.

While P3b latency appears to be a sensitive biomarker for PD dementia (PDD), the data accumulated and reviewed here do not support previously suggested hypotheses with regard to the moderating factors of the prolongation of P3b latency in PD. For instance, Hayashi et al. (1996) proposed that P3b latency prolongation depends on disease severity, and Kutukcu et al. (1998) suggested that P3b in non-demented PD patients is only prolonged when overt responses are required. However, even when we excluded samples involving demented patients from the analysis, the likelihood of significant P3b prolongation was neither affected by HY stage ($\chi^2(1, n = 37) = 0.59$, $p = 0.44$), nor by response mode ($\chi^2(1, n = 46) = 1.31$, $p = 0.25$; in fact, studies were numerically more likely to yield significant group differences when they did not require participants to make an overt response). In sum, there is reliable evidence for prolongation of P3b latency in demented, but not in non-demented PD patients, suggesting that a decrease in the speed of stimulus evaluation occurs in PDD, but not in PD.

2.1 P3b and the specificity of cognitive changes in PD

Having established that P3b latency is sensitive to dementia in PD, it should not be surprising to find associations between P3b latency and global measures of cognitive ability in PD patients. The degree of global cognitive impairment has been linked to P3b latency by studies

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showing correlations between P3b latency and neuropsychological measures of general intelligence (Bodis-Wollner et al., 1995; Hansch et al., 1982; Katsarou et al., 2004), processing speed (O'Donnell et al., 1987), and, most frequently, the global score on the MMSE (Lukhanina et al., 2009; Maeshima et al., 2002; Matsui et al., 2007; Sartucci et al., 1990; Stamenović et al., 2005; Tachibana et al., 1997; but see Elwan et al., 1996; Lukhanina et al., 2008).

Some studies have also evaluated the relationship between P3b latency and cognitive functions that might be indicative of specific fronto-striatal alterations. Specifically, P3b latency appears to be related to prototypical executive functions such as set-shifting (Iijima et al., 2000; Katsarou et al., 2004; Stamenović et al., 2005; but see Stanzione et al., 1998), trail-making (Matsui et al., 2007; Stamenović et al., 2005; but see Elwan et al., 1996), verbal fluency (Bodis-Wollner et al., 1995; Chen et al., 2006), working memory (O'Donnell et al., 1987), and planning (Kim et al., 1995), even in non-demented patients. However, to date it is not clear whether the association between P3b latency and executive functioning in PD is actually specific, because previous studies did not control for the variance shared with measures of global cognitive ability. Future studies involving larger samples sizes and neuropsychological test batteries are required to establish whether P3b latency relates to distinct or generalized alterations in cognitive functioning in PD.

Along similar lines, more data are needed to support the notion that P3b latency prolongation can serve as a diagnostic tool to differentiate PD or PDD from other types of dementia or parkinsonian syndromes. P3b latency has been found to be prolonged in multiple system atrophy (MSA; Deguchi et al., 2001; Kamitani et al., 2002; Kamitani and Kuroiwa, 2009), corticobasal degeneration (CBD; Takeda et al., 1998; Wang et al., 2000), progressive supranuclear palsy (PSP; Pierrot-Deseilligny et al., 1989; Takeda et al., 1998), dementia with Lewy bodies (DLB; Kurita et al., 2010), and Alzheimer's disease (AD; Golob and Starr, 2000;

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Olichney et al., 2011; Polich et al., 1990). Only a few studies have recorded the P3b in more than

a single group of patients to allow for direct comparison of P3b latency across diagnostic groups.

In general, P3b latency prolongation, while being related to the progression of cognitive decline

in different types of dementia (Polich et al., 1986), does not seem to differ between AD and PDD

patients (Filipović et al., 1990; Hanafusa et al., 1991; Tachibana et al., 1992; but see Goodin and

Aminoff, 1986). However, more recent work by Kurita et al. (2010) suggests that P3b latency

prolongation might in fact be more pronounced in PDD than in AD, especially in those PDD

patients who suffer from visual hallucinations.

A further promising study involving non-demented patients suffering from different

parkinsonian syndromes demonstrated that P3b latency was only prolonged in CBD, but not in

non-demented PD or PSP patients, while P3b amplitude was selectively decreased in PSP

patients (Wang et al., 2000). Whereas the dissociation regarding P3b latencies was not replicated

in a study with a similar design (Pirtošek et al., 2001), P3b amplitude appears to be reproducibly

larger in non-demented PD patients when compared to patients suffering from PSP (Johnson,

1995; Pirtošek et al., 2001). Clearly, however, more comparative studies involving sufficient

sample sizes are required to establish the utility of P3b amplitude measures in differentiating PD

and PSP. Most other approaches to use P3b measures for differential diagnosis were rather

exploratory and were not followed up by systematic replication. In the study by Antal et al.

(2000), P3b latency was substantially prolonged in PD patients, but not in patients suffering from

essential tremor (ET). More recent work by Balaban et al. (2012) demonstrated, however, that ET

patients also showed marked prolongations of P3b latency. Moreover, P3b latency appeared to be

shorter in juvenile PD when compared to idiopathic PD patients (Kaseda et al., 1996), while the

extent of P3b latency prolongation was observed to be similar in idiopathic PD and vascular PD

patients (Oishi et al., 1996). However, in the study by Oishi et al. (1996), P3b latency was

reduced by levodopa administration in idiopathic PD, but not in vascular PD. This latter finding illustrates a further potential field of application for P3b measures: the study of medication effects on cognitive functioning in PD.

2.2 P3b and dopaminergic medication in PD

Investigations comparing P3b measures in PD patients on and off medication have been used (a) to improve the understanding of dopaminergic involvement in PD-related cognitive deficits (Růžička et al., 1994) and (b) as a human model to study dopaminergic contributions to P3b generation (Stanzione et al., 1991). In most of the studies on levodopa effects, never-medicated PD patients or patients who underwent a drug washout period (12 h – 14 days) were tested on an oddball procedure, first off and then on medication. We identified nine studies employing such a study design with five of them demonstrating a reduction of P3b latency following levodopa administration (Lukhanina et al., 2009; Oishi et al., 1996; Sohn et al., 1998; Stanzione et al., 1991; Starkstein et al., 1989). However, P3b latency was not significantly decreased by levodopa in the studies by Chia et al. (1995), Kobayashi et al. (2004), and Mathis et al. (2014) and even increased under levodopa in the study by Prasher and Findley (1991). Although the majority of these studies suggest that PD-related P3b latency prolongation is normalized by levodopa, this finding is far from reliably established. First, none of the studies employed a placebo-controlled design or an on vs off medication counterbalancing procedure controlling for order effects. Hence, medication effects were always confounded with potential effects of learning, fatigue or habituation. In a recent study that controlled for these factors (Georgiev et al., 2015), no differences in P3b latency have been found as a function of PD patients' dopaminergic status (see also Vieregge et al., 1994). Second, it has to be noted that sample sizes were considerably smaller in the studies reporting a levodopa-associated decrease in P3b latency (mean $N = 14.8$) than in the studies reporting no such effect (mean $N = 23.5$; $p_{one-tailed}$

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$_{t\text{-test}} = 0.03$), thus challenging the reliability of the proposed levodopa effect. With regard to P3b amplitude, no differences associated with levodopa treatment in PD have been reported to date.

Only a few studies are available on the effects of dopamine agonists on P3b latency in PD. While neither amplitude nor latency of the P3b was altered by bromocriptine administration (Rumbach et al., 1993), apomorphine appeared to increase P3b latency and to decrease P3b amplitude (Růžička et al., 1994, 1998). Notably, ERP measures were negatively affected in the latter studies while substantial motor improvements were observed following drug administration, indicating that P3b might potentially qualify as an objective indicator of the cognitive side effects of dopamine agonists. Moreover, in a more controlled, experimental design P3b latency was surprisingly found to be prolonged in PD patients under the influence of the peptide hormone cholecystokinin, which is thought to increase dopaminergic firing in the basal ganglia (Smolnik et al., 2002).

Medication studies targeting non-dopaminergic mechanisms identified shortened P3b latencies following administration of the glutamate antagonist amantadine (Bandini et al., 2002), while P3b measures appeared not to be affected by the noradrenergic agonist naphtoxazine (Bédard et al., 1998). More recent studies have also focused on the effect of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on scalp-recorded P3b amplitudes of PD patients (Gerschlager et al., 2001; Kovacs et al., 2008; Naskar et al., 2010). P3b latency and amplitude have been found to be unaffected by STN DBS in all of these studies.

In summary, the lack of consistent effects of both dopaminergic medication and STN DBS on P3b measures in PD suggests that the cognitive mechanisms reflected by the P3b might not depend to a crucial extent on the integrity of dopaminergic pathways. Specifically, PD-related P3b latency prolongation cannot easily be attributed to nigro-striatal dopamine depletion, a conclusion that is further supported by the evidence reviewed above that P3b latency alterations

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are predominantly observed in PDD patients for whom signs of neurodegeneration involve wide areas of the neocortex (Wolters and Braak, 2006).

2.3   P3b in PD: conclusions and future directions

Over the last decades, the study of cognitive ERPs in PD was largely dominated by an interest in potential P3b alterations and their functional significance. The evidence from a large number of independent investigations can be summarized as the prolongation of P3b latency being sensitive to the presence of dementia in PD, whereas P3b latency is not generally prolonged in non-demented PD patients (Fig. 3, left panel). P3b latency prolongation cannot easily be reversed by means of dopamine replacement therapy or DBS, and it is not specifically related to executive function deficits, which are characteristic of fronto-striatal dysfunction in PD. Congruent with the prevailing interpretation of P3b latency as a measure of stimulus evaluation time, P3b latency prolongation might rather serve as a sensitive biomarker for global cognitive decline as it occurs in PDD. However, P3b latency prolongation is not a specific feature of PDD, as it can also be observed in other dementing diseases, including Alzheimer's disease, and atypical parkinsonian syndromes.

Future investigations of P3b latency prolongation in PD should explore the moderators of this effect, i.e., clarify under which conditions P3b latency is prolonged in PD. Studies addressing this question might benefit from manipulating the demands for stimulus evaluation. For instance, stimulus evaluation time (as mirrored in P3b latency) is typically shorter when target stimuli occur in a predictable manner; however, this shortening of latency by predictability does not occur in PD patients (Fogelson et al., 2011). Similarly, PD-related P3b latency prolongation has been shown to depend on the choice of the task-relevant stimulus dimension (with prolonged motion discrimination time and normal color discrimination time in PD patients) and thus on the recruited processing pathways within the visual system (Arakawa et al., 1999).

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In contrast to its latency, P3b amplitude has generally been found to be unaltered in PD patients, even in those suffering from dementia. While indicating that PD patients do not seem to have difficulties allocating processing resources to relevant target stimuli in the oddball paradigm, this finding is not particularly surprising. The detection of clearly identifiable target stimuli in the absence of any conflicting information is certainly not the ideal task to tax those cognitive processes that may be impaired in PD or in PDD. In the future, P3b investigations that are tailored to PD-related cognitive deficits may be more promising.

A recent example of such a study has been reported by Verleger et al. (2013) who measured the P3b in a flanker paradigm (Fig. 1) not only in the conventional way (i.e., stimulus-synchronized), but also time-locked to the participants' responses. In healthy controls, stimulus- and response-locked P3b amplitudes were indistinguishable, suggesting that the associated stimulus-response links (possibly supported by the basal ganglia) were largely intact. However, in PD patients, response-locked amplitudes were substantially smaller than stimulus-locked potentials, and the authors attributed the response-locked P3b amplitude attenuation in PD patients to nigro-striatal dopamine depletion.

In a further study (Münte et al., 2015), P3b has been recorded in a dual-task paradigm to test the hypothesis that PD may be associated with decreased attentional processing capacity. PD patients and healthy controls were presented with a classical two-stimulus oddball procedure as a secondary task while they also completed a primary task that placed either high (random number generation; participants were asked to press number keys in a random order) or low (ordered number generation; participants are asked to press number keys in a canonical order) demands on participants' processing capacities. In healthy controls rare target stimuli in the oddball task elicited P3b waveforms of similar amplitude in the high-demanding and in the low-demanding

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task. In PD patients, however, P3b amplitude was selectively decreased in the more demanding version of the primary task, indicating a PD-related limitation of attentional processing resources.

The data that were obtained from these two studies illustrate that P3b amplitudes might indeed provide interesting insights about neural and cognitive dysfunctions associated with PD. One prerequisite for successful P3b-based ERP studies of PD is to tailor experimental designs and data analyses toward specific hypotheses about PD-related neural and cognitive alterations.

3   P3a, mismatch negativity, and reorienting negativity: novelty processing and deviance detection

PD patients may have difficulties shifting attention and adapting to novelty in the environment (Dubois and Pillon, 1997; Rustamov et al., 2014). Hence, investigating ERP responses related to attentional processes in PD patients may be of particular relevance for understanding some of the cognitive changes associated with the disease. In this context, previous research has focused on the assessment of the P3a waveform in the three-stimulus oddball task (Fig. 1) as well as in the distraction paradigm (see below).

Specifically, P3a measures have been analyzed in about a dozen studies involving patients with PD (Table 2). The emerging findings are rather heterogeneous. While only two studies reported prolonged P3a latencies in PD, it is remarkable that neither of these studies reported PD-related P3b prolongation in response to target oddball stimuli (Tsuchiya et al., 2000; Zeng et al., 2002), suggesting a potential dissociation between P3a and P3b latency in PD. This dissociation is further supported by the observation that P3a latency does not seem to differ between PDD patients and PD patients without dementia (Tachibana et al., 1992; Toda et al., 1993).

P3a amplitude has been found to be attenuated in PD in some studies (Li et al., 2005; Solís-Vivanco et al., 2011, 2015; Tsuchiya et al., 2000; Wang et al., 1999, 2000), but not in others (Bocquillon et al., 2012; Gaudreault et al., 2013; Georgiev et al., 2015; Hozumi et al.,

2000; Pirtošek et al., 2001; Tachibana et al., 1992; Toda et al., 1993; Zeng et al., 2002). These differences can hardly be explained by different task characteristics, as, for instance, the studies by Tachibana et al. and Toda et al. (no amplitude reduction) used the same procedures as the studies by Li et al. and Wang et al. (significant amplitude reduction). It seems more likely that the PD-related P3a amplitude attenuation constitutes a medium-sized effect that sometimes fails to reach significance due to insufficient statistical power (Cohen, 1992). Enhanced P3a amplitudes in oddball tasks have been interpreted to indicate stronger distractibility in several clinical populations (Escera et al., 2000). In addition, smaller P3a amplitudes obtained from three-stimulus oddball tasks have been associated with more efficient performance in more demanding tasks (Lange et al., 2015). Against this background, PD-related attenuation of P3a amplitudes in three-stimulus oddball tasks may indicate enhanced resistance to distraction in PD patients. Alternatively, reduced P3a amplitudes may reflect a PD-related impairment in directing attention to potentially important changes in the environment (Barry et al., 2011).

The functional significance of orienting responses to novel stimuli is illustrated by a study by Schomaker et al. (2014). In this study, patients and controls were required to memorize words that were either presented in a standard font or in one of multiple novel fonts. Healthy controls showed the typical von Restorff effect (i.e., better memory for words that were written in novel fonts; von Restorff, 1933). In contrast, PD patients did not benefit from the word being written in a novel font. Likewise, P3a amplitudes were enhanced in response to novel font words in controls, but not in PD patients, suggesting that patients have difficulties allocating attentional resources to novel features (Schomaker et al., 2014).

The adaptive nature of attentional orienting is further illustrated by the sensitivity of P3a amplitude to habituation. As a cortical correlate of the orienting response, the P3a amplitude decreases with an increasing number of stimulus repetitions (Friedman et al., 2001). This

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habituation is entirely lacking in PD patients (Tsuchiya et al., 2000), thereby mirroring the pattern observed in patients with dorsolateral prefrontal cortex lesions (Knight, 1984). In this context, it is remarkable that the PD-related P3-amplitude attenuation has been related to perseverative behavior on the Wisconsin Card Sorting Test (WCST; Heaton et al., 1993), a well-established neuropsychological test of cognitive flexibility (Tsuchiya et al., 2000). Perseverative tendencies on this test are commonly regarded as a hallmark of executive dysfunctions in both PD patients (Dirnberger and Jahanshahi, 2013; Gotham et al., 1988) and patients with prefrontal cortex lesions (Demakis, 2003; Milner, 1963). In conclusion, P3a amplitude attenuation in PD patients may be an electrophysiological correlate of PD-related behavioral deficits in adjusting rapidly and efficiently to novel environmental demands, an executive function that is supported by the integrity of fronto-striatal loops (Monchi et al., 2001, 2004).

Another recent finding that underscores the functional relevance of P3a in PD has been reported by Solís-Vivanco et al. (2015). These authors found the degree of P3a amplitude attenuation in 55 PD patients to be linearly related to disease duration, even when controlling for covariates such as age and MMSE score. This finding has been suggested to indicate that P3a amplitude may qualify as a reliable biomarker of disease progression (Solís-Vivanco et al., 2015). Along similar lines, the P3a amplitude attenuation has been found to be associated with apathy (Mathis et al., 2014) and akinesia (Wang et al., 2000) in PD patients. Further studies investigating P3a amplitude attenuation in PD and the links between this ERP measure and clinical or cognitive variables are essential for establishing the utility of P3a measurement for an understanding of neural and cognitive sequelae of PD.

However, the utility of P3a amplitude measures for differential diagnosis seems limited. In the study by Wang et al. (2000), the P3a was reduced in PD, but not in CBD, while the opposite pattern was observed by Pirtošek et al. (2001). Interestingly, however, P3a latency, but

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not P3a amplitude or P3b measures, significantly differed between PDD patients and AD patients (Tachibana et al., 1992).

When the P3a is recorded in the distraction paradigm (Schröger and Wolff, 1998), as for example in the studies by Solís-Vivanco et al. (2011, 2015), it is typically preceded by the Mismatch Negativity (MMN), an index of relatively automatic deviance detection (Näätänen et al., 2007). In the distraction paradigm, participants are instructed to attend to one stimulus dimension (e.g., tone duration), while the presented stimuli also vary on a second, task-irrelevant dimension (e.g., tone pitch). Unexpected changes in the task-irrelevant stimulus dimension (e.g., a rare high-pitched tone in a series of frequent low-pitched tones) elicit the MMN. Alternatively, the MMN can also be recorded in response to oddball stimuli when participants are asked to ignore the oddball sequence (e.g., Karayanidis et al., 1995; Pekkonen et al., 1995). Further, in the distraction paradigm, MMN and P3a are followed by the Reorienting Negativity (RON) that is related to reorienting attention toward performing the task following distraction (Schröger and Wolff, 1998).

Overall, studies of MMN in PD do not point to a pronounced disease-related deficit in pre-attentional mechanisms of deviance detection (Table 2). Although MMN amplitude in response to deviant sounds has been reported to be attenuated in non-demented PD patients in one study (Pekkonen et al., 1995), no such differences could be found in six other studies (Brønnick et al., 2010; Karayanidis et al., 1995; Pekkonen et al., 2000; Solís-Vivanco et al., 2011, 2015; Vieregge et al., 1994). However, in the study by Brønnick et al. (2010), MMN amplitude was markedly attenuated in PDD patients and, surprisingly, the extent of the MMN attenuation was more pronounced in PDD patients than it was in AD or DLB patients. Hence, MMN amplitude reduction might share the sensitivity of P3b latency prolongation for PDD (see above) without suffering from a lack of specificity.

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With regard to RON, only limited data have been reported so far. No differences in the

RON amplitude have been observed when PD patients were on dopaminergic medication (Solís-

Vivanco et al., 2011; Solís-Vivanco et al., 2015). However, the RON amplitude was significantly

reduced in non-medicated patients when compared to both medicated patients and healthy

controls (Solís-Vivanco et al., 2011). Hence, the RON amplitude might be susceptible to

dopaminergic influence. Future studies employing the distraction paradigm in PD patients

varying in presence/absence of dementia and medication status are needed to further investigate

the differential sensitivity of MMN and RON to the presence of PDD and to variations in

dopamine activity, respectively.

3.1   P3a, MMN, and RON in PD: conclusions and future directions

In contrast to the good evidence for P3b latency prolongation in PDD, the available MMN

data are much less clear-cut, but they suggest that MMN amplitude may be attenuated in PDD in

a nosologically specific manner. The RON obtained from distraction paradigms potentially

provides a state marker of nigro-striatal dopamine depletion in PD (Solís-Vivanco et al., 2011).

Overall, the P3a amplitude findings in PD must be considered equivocal, and it appears that

differences between PD patients and controls are not very large. Researchers interested in

studying this waveform in PD should focus on systematically deducted research questions, and

tailor their paradigms to precisely answer these questions. Studies should be conducted in large

samples to obtain a reliable estimate of the effect sizes. One study (Solís-Vivanco et al., 2015)

reported an association between P3a amplitude attenuation and disease duration in PD. Future

studies employing longitudinal designs are required to examine the utility of P3a amplitude as a

biomarker of disease progression in PD.

4   NoGo-P3, N2, and error(-related) negativity: executive control

The Go/NoGo task (Fig. 1) is among the standard tasks to examine executive control in PD. ERPs measured in Go/NoGo tasks consist of more pronounced stimulus-synchronized negative deflections (NoGo-N2) and a subsequent positivity (NoGo-P3) in NoGo-trials as compared to Go-trials with a fronto-central scalp topography. Fronto-centrally distributed stimulus-synchronized (conflict-)N2 waveforms are also observed in conflict (or interference) tasks (such as the Eriksen flanker task, see Fig. 1). Thus, both the NoGo-N2 and the N2 elicited in interference tasks have been claimed to indicate the resolution of response conflict by executive control processes (Kopp et al., 1996a,b). Incorrect responses in various choice-response tasks are typically followed by a prominent N_e/ERN, i.e., a fronto-centrally distributed, response-synchronized negative deflection in ERP waveforms. The N_e/ERN provides a neurophysiological indicator of the integrity of neural networks for performance monitoring (Ullsperger et al., 2014a).

4.1   NoGo ERPs: response conflict and inhibition

As will be seen, the studies assessing ERPs in Go/NoGo tasks (Pires et al., 2014; see Fig. 1) in PD differ considerably with regard to the statistical comparisons which they report (Table 3). Some studies report group main effects on ERP amplitudes and latencies (i.e., disregarding potential differences between Go-ERPs and NoGo-ERPs), whereas other studies report trial-specific effects (e.g., Go-P3, NoGo-P3). Furthermore, some studies refer to the difference potential that is obtained by subtracting Go-ERP amplitudes or latencies from the respective NoGo-ERP measures (i.e., NoGo – Go). This heterogeneity between studies hinders comparisons between and conclusions from the studies; more standardization would increase the comparability between studies and would be desirable.

In the Go/NoGo task (Fig. 1), participants are asked to respond to some stimuli ('Go'-trials) and to refrain from responding to other stimuli ('NoGo' trials). Due to the usually large

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proportions of Go-trials, the participants develop a predominant tendency to respond that places high demands on executive processes of action restraint on NoGo-trials (Eigsti et al., 2006; Lange et al., 2014; Lange and Eggert, 2015). As displayed in Table 3, NoGo-P3 amplitudes were repeatedly reported to be attenuated in PD patients (Beste et al., 2009a; Bokura et al., 2005; Osawa et al., 2005; Pulvermüller et al., 1996; but see Beste et al., 2010). Note that Beste et al. (2009a), Bokura et al. (2005), and Pulvermüller et al. (1996) studied PD patients on their dopaminergic medication, whereas Beste et al. (2010) reported results that were obtained from PD patients off their dopaminergic medication. P3 latencies did not differ significantly between controls and PD patients in the two studies by Beste et al. (2009a, 2010). The difference between NoGo-P3 latencies minus Go-P3 latencies was enhanced in PD patients in the study by Beste et al. (2009a); however, the effect was confined to a version of the Go/NoGo task which involved semantic incompatibility between stimuli and responses (i.e., 'STOP' signaled Go-trials and 'PRESS' signaled NoGo-trials), thereby posing particularly high demands on executive control. Moreover, Bokura et al. (2005) found prolonged NoGo-P3 latencies in PD patients, whereas Go-P3 latencies did not differ from those observed in controls.

Two ERP studies in PD patients employing Go/NoGo tasks revealed generally enhanced (i.e., more negative) N2 amplitudes in patients with PD (Beste et al., 2009a, 2010). These studies differ with regard to the precise N2 amplitude effects: While Beste et al. (2009a) found enhanced NoGo-N2 amplitudes in PD, the later study by Beste et al. (2010) reported unaltered NoGo-minus-Go N2 amplitude differences in PD. Yet another study showed attenuated NoGo-minus-Go N2 amplitude differences in PD (Bokura et al., 2005). Only one study found N2 latencies to be generally prolonged in PD patients (Beste et al., 2009a), whereas the NoGo-minus-Go N2 latency differences appear to be unaltered in PD (Beste et al., 2009a; Bokura et al., 2005).

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To conclude, the available studies assessing ERPs in Go/NoGo tasks yielded quite inconsistent findings, with the sole exception that four studies reported attenuated NoGo-P3 amplitudes in PD. The only study that did not report attenuated NoGo-P3 amplitudes in PD patients looked at PD patients off their dopaminergic medication (Beste et al., 2010). A reasonable integration of these data across studies is, however, hampered by the heterogeneity of study designs and ERP measures.

4.2 N2: conflict processing

ERP indicators of conflict processing are usually examined in interference tasks in which automatic processes interfere with the selection of task-relevant responses. A prominent example is the Stroop task (Stroop, 1935). Here, the identity of a color word can interfere with the participants' ability to name the color in which the word is displayed. For example, saying "green" (i.e., the task-relevant response) in response to the word "red" (triggering the task-irrelevant response of saying "red") written in green ink is more difficult compared to saying "green" in response to the word "green" written in green ink. In this latter case, the task-relevant response is identical to the task-irrelevant response. However, there is no ERP study of conflict processing in PD which relied on the Stroop task. Table 4 provides details of the available ERP studies which examined conflict processing using other interference tasks in PD.

4.2.1 Simon task

The Simon effect (Simon and Rudell, 1967) refers to the finding that spatially arranged responses to non-spatial stimulus features (such as shape, color etc.) are faster when the task-irrelevant stimulus location and response location correspond compared to when they do not correspond (Leuthold, 2011). For instance, the participant is asked to press a key using the left hand when a blue stimulus occurs and to press another key using the right hand when a red stimulus occurs. Reactions are typically slower and more errors occur when the stimulus is

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displayed contralaterally to the correct response hand. To date, only one study examined N2 amplitudes in PD patients using a Simon task that reported reduced N2 amplitudes in PD (Praamstra and Plat, 2001).

4.2.2 Flanker task

In the flanker task (Eriksen and Eriksen, 1974; Kopp et al., 1996b; Seer et al., 2015), a central target stimulus (e.g. '>') serves as the task-relevant stimulus which is surrounded by either congruent ('> > > > >') or incongruent ('< < > < <') task-irrelevant distractor stimuli, and the typical finding is that the automatic processing of task-irrelevant distractors interferes with the selection of task-relevant responses. Pronounced fronto-central N2 waveforms are observable on incongruent trials of the flanker task (Danielmeier et al., 2009; Folstein and Van Petten, 2008; Kopp et al., 1996b; Yeung et al., 2004). Fronto-central N2 waveforms are not only sensitive to congruency; they are also modulated by the congruency sequence across successive trials: N2 amplitudes on incongruent trials are attenuated when the preceding trial was incongruent compared to when the preceding trial was congruent (Clayson and Larson, 2011a,b, 2012; Forster et al., 2011; Larson et al., 2012). This contextual modulation of N2 amplitudes has been attributed to an adaptation to the presence or absence of environmental conflicts, respectively ('conflict adaptation', Botvinick et al., 2001; for detailed discussion, see Egner, 2007).

Inspection of Table 4 reveals that N2 amplitudes in the flanker task have repeatedly been found unaltered in chronically medicated PD patients (Praamstra et al., 1998; Stemmer et al., 2007; Verleger et al., 2010; Willemssen et al., 2011). Similarly, congruency affects N2 amplitudes normally in chronically medicated PD patients, with larger N2 amplitudes elicited on incongruent compared to congruent trials (Rustamov et al., 2013). However, one study found attenuated N2 amplitudes on incongruent trials in asymptomatic (and hence non-medicated) carriers of *Parkin* or *PINK1* mutations who are considered to represent pre-clinical PD patients

(Verleger et al., 2010). In a similar vein, Willemssen et al. (2011; de novo | pre medication) found diminished N2 congruency effects in a group of newly diagnosed, drug-naive PD patients. Following the initiation of dopaminergic medication, N2 congruency effects no longer differed from that observed in a control group, potentially indicating that dopaminergic medication might remedy altered N2 congruency effects in drug-naive PD patients (Willemssen et al., 2011; de novo | post medication). Thus, the role of dopaminergic medication on N2 congruency effects in PD remains to be clarified in future studies. In particular, the effects of medication should be disentangled from learning effects; these two factors were (necessarily) confounded in the study by Willemssen et al. (2011) in which the patients were always drug-naive at initial testing, and always medicated at subsequent testing.

Other ERP measures (N2 latencies: Praamstra et al., 1998; Rustamov et al., 2013; Willemssen et al., 2011; P3 amplitudes and latencies: Praamstra et al., 1998; Stemmer et al., 2007; Willemssen et al., 2011; but see Verleger et al., 2013) were unaltered in PD when examined in flanker tasks. Overall, the evidence suggests that electrophysiological correlates of conflict processing are unaltered in medicated PD patients. However, it remains to be delineated whether N2 amplitude congruency effects provide a biomarker of nigro-striatal dopamine depletion in PD that is counteracted by dopaminergic medication.

The contextual modulation of N2 amplitudes in the flanker task was found to be attenuated in medicated PD patients (Rustamov et al., 2013). Specifically, control participants showed the typical congruency sequence effect, i.e., substantially enhanced N2 amplitudes on incongruent trials when the preceding trial was congruent compared to when the preceding trial was incongruent. In contrast, N2 amplitudes were not differentially affected by the congruency sequence in PD patients. This finding may suggest that conflict adaptation is disturbed in PD; however, the functional significance of the congruency sequence effect is subject to debate (for

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detailed discussion, see Rustamov et al., 2013). Another study (Rustamov et al., 2014) combined the flanker task with attentional set shifting such that central or peripheral stimuli were task-relevant throughout short series of trials after which the spatial location of the task-relevant stimulus was altered back and forth. Control participants showed strong evidence for contextual modulation of ERPs across these series of trials. Specifically, N2 and P3 amplitudes on incongruent trials were enhanced on shift trials, and both amplitudes gradually decreased across repetition trials. In contrast, medicated PD patients did not show evidence for this contextual modulation of N2 and P3 amplitudes. Taken together, these two studies suggest that the analysis of contextual modulation of ERPs in the flanker task might be a more promising tool than the effects of flanker congruency on ERPs in PD.

4.3 N_e/ERN: performance monitoring

The flanker task has been frequently used to assess electrophysiological correlates of performance monitoring, most frequently the error negativity (N_e; Falkenstein et al., 1990; Falkenstein et al., 1991) or error-related negativity (ERN; Gehring et al., 1993). The N_e/ERN is an early negative deflection in response-synchronized ERP waveforms occurring at fronto-central scalp regions shortly after erroneous responses. Correct responses are also associated with a somewhat less pronounced response-synchronized negative waveform, which has been termed correct negativity (N_c) or correct-related negativity (CRN; Falkenstein et al., 2000; Vidal et al., 2000). Erroneous responses further elicit positive response-synchronized waveform deflections which are referred to as error positivity (P_e; Falkenstein et al., 1990; Falkenstein et al., 1991). The P_e can be subdivided into an early, fronto-centrally distributed P_e and a late, parietally distributed P_e (Ullsperger et al., 2014a). Finally, a response-synchronized positive waveform deflection occurs after correct responses (P_c; e.g., Ito and Kitagawa, 2006; Olvet and Hajcak, 2012).

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Table 5 shows the available N_e/ERN and N_c/CRN studies in PD. Attenuated N_e/ERN amplitudes in PD patients have been repeatedly reported (for an earlier overview, see Jocham and Ullsperger, 2009), most notably in the flanker paradigm (Beste et al., 2009b; Falkenstein et al., 2001; Rustamov et al., 2014; Stemmer et al., 2007; Willemssen et al., 2008, 2009), but also in the Simon task (Falkenstein et al., 2001), in the Go/NoGo paradigm (Falkenstein et al., 2001), and in a lexical decision task (Ito and Kitagawa, 2006). Only two studies reported unaltered N_e/ERN amplitudes in PD (Holroyd et al., 2002; Verleger et al., 2013). It seems likely that the absence of statistically significant group differences is a result of the small samples sizes used in these studies. In fact, given the rather low statistical power associated with typical ERP studies in PD, the obtained pattern of results (11 out of 13 studies reporting significant group differences) is statistically more credible than one with 13 out of 13 studies reporting significant group differences (this latter pattern would rather suggest selective reporting of positive findings; Schimmack, 2012). In contrast, N_e/ERN latencies do not seem to be altered by PD (Beste et al., 2009b; Ito and Kitagawa, 2006; Verleger et al., 2013; Willemssen et al., 2009). Falkenstein et al. (2001) found decreased N_e/ERN latencies in PD using a Simon task, but N_e/ERN latencies were unaltered in the same patients in a flanker task and in a Go/NoGo task. This pattern (no PD-related N_e/ERN latency difference in four studies, latency decrease in one single task on a multiple-task study) is compatible with random error variance around a null effect.

N_c/CRN amplitudes have been found unaltered in four studies (Beste et al., 2009b; Falkenstein et al., 2001; Ito and Kitagawa, 2006; Willemssen et al., 2008), whereas one study found enhanced N_c/CRN amplitudes in PD patients (Willemssen et al., 2009). N_c/CRN latencies were consistently found to be unaffected by PD (Beste et al., 2009b; Falkenstein et al., 2001; Ito and Kitagawa, 2006; Willemssen et al., 2009). Falkenstein et al. (2001) assessed late P_e amplitudes in PD patients using a flanker task, a Simon task, and a Go/NoGo task, and they did

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not find differences between PD patients and control participants. However, Ito and Kitagawa (2006) reported attenuated early P_e and P_c amplitudes in PD patients, whereas early P_e and P_c latencies were normal.

4.4 N_e/ERN and dopaminergic medication in PD

The reviewed body of evidence reveals disturbed neural activities for performance monitoring in PD, as assessed by N_e/ERN amplitudes. However, additional work is required to dissect the relative effects of disease and dopaminergic treatment on performance monitoring in PD. It is well recognized that the relation between dopamine and performance follows an inverted U-shaped function, implying that both insufficient and excessive levels of dopamine impair performance on cognitive tasks (Cools and D'Esposito, 2011; Fallon et al., 2013; Gotham et al., 1988). In early clinical stages of PD, the degeneration of dopamine-producing cells is most pronounced in the substantia nigra, leading to severe dopamine depletion in the dorsal striatum, whereas mesocortical dopamine projections as well as ventral cortico-striatal loops are less affected (see Introduction). Dopaminergic replacement therapy, administered to alleviate motor symptoms associated with the affected dorsal cortico-striatal loops, can at the same time impair, through overdosing, functions relying on otherwise intact prefrontal (Gotham et al., 1988) and ventral cortico-striatal loops (Cools, 2006). Thus, it remains a possibility that most of the relevant N_e/ERN findings occurred as a corollary of excessive levels of dopamine in the prefrontal cortex and/or in the ventral striatum in medicated PD patients, rather than consequent to dopamine depletion in the dorsal striatum (Rustamov et al., 2014).

Inspection of Table 5 reveals that the majority of relevant results was obtained from medicated PD patients and may thus be confounded by excessive levels of dopamine in the prefrontal cortex and/or in the ventral striatum due to dopaminergic medication. However, there are three studies which examined N_e/ERN amplitudes in never-medicated PD patients (Beste et

al., 2009b; Stemmer et al., 2007; Willemssen et al., 2009) and three studies of PD patients who underwent a drug washout period (i.e., were tested after overnight withdrawal; Beste et al., 2009b; Holroyd et al., 2002; Willemssen et al., 2008). Except the study by Holroyd et al. (2002), all these studies revealed attenuated N_e/ERN amplitudes in PD patients who were either drug-naive or off dopaminergic medication, suggesting that insufficient levels of dopamine disturb neural activities for performance monitoring.

Direct comparisons between PD patients on and off (or drug-naive) dopaminergic replacement therapy are scarce. Willemssen et al. (2008) studied 18 PD patients at early stages of the disease (mean UPDRS Part III on medication = 10.8; off medication = 14.8). These authors conducted intra-individual comparisons, and they counterbalanced the order of on-medication and off-medication testing. No effects of acute dopaminergic medication on N_e/ERN amplitudes could be discerned. The studies which compared drug-naive PD patients with chronically medicated PD patients did not report N_e/ERN amplitude differences between these groups, neither when the latter patients were on medication (Stemmer et al., 2007) nor when they were off medication (Beste et al., 2009b) during testing. In a more recent study, Siegert et al. (2014) found differential effects of dopaminergic therapy on task performance in a flanker task depending on the patients' age and disease onset, supporting a dopamine overdose effect in younger patients with early onset of PD; these behavioral changes corresponded to the modulation of N_e/ERN amplitudes.

4.5   NoGo-P3, N2, and N_e/ERN: conclusions and future directions

From the reviewed body of evidence about ERP correlates of executive dysfunctioning in PD there is reasonably good evidence for attenuated NoGo-P3 amplitudes in medicated PD patients. The N2 data are much less clear-cut, but they point in the direction that N2 amplitudes might be attenuated in individuals at risk for developing PD (i.e., pre-symptomatic carriers of

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gene mutations associated with PD) as well as in drug-naive, but not in chronically medicated PD patients. Thus, N2 amplitudes have the potential to provide a biomarker of nigro-striatal dopamine depletion in PD. An analysis of the contextual modulation of N2 amplitudes in the flanker paradigm is a promising candidate for further experimentation in that direction. Overall, the N_e/ERN amplitude findings in PD provide the most compelling evidence for a disturbance in the neural substrates of executive functions in PD (Fig. 3, right panel). Taken together, the reviewed N_e/ERN data imply that both insufficient and excessive levels of dopamine impair performance monitoring in PD. We depict our main conclusions from this review of the literature in Fig. 4 (left panel).

5   Approaches exploring ERPs in other cognitive domains

5.1   Language

Language processing in PD has been investigated against the background of the influential declarative/procedural model of language (Ullman, 2001). The model holds that the (declarative) mental lexicon is represented in temporal cortical areas while the (procedural) mental grammar relies on the integrity of frontal cortex and the basal ganglia. In accordance with this idea, patients suffering from PD appear to have difficulties in syntactic, but not semantic language processing (Friederici et al., 2003). ERP analysis has been proven to be highly useful in generating evidence for this dissociation. Compared to sentences in which the final word meets the individual's expectations (e.g., "The shirt has been ironed."), when the final word of a sentence is semantically incongruent (e.g., "The thunderstorm has been ironed."), these incongruent word stimuli typically elicit a centroparietal negativity, the N400 (Kutas and Hillyard, 1980). In contrast, syntactical violations (e.g., the "to" in "The mother induced to watch the children.") are followed by a centroparietal positivity, the P600, in comparison to syntactically correct events (e.g., the "to" in "The mother agreed to adopt the child.") (Osterhout

and Holcomb, 1992). Hence, the N400 and P600 can be regarded as electrophysiological correlates of semantic and syntactic processing, respectively. In a group of medicated, non-demented PD patients, the N400 was found to be unaltered, while the P600 appeared to be modulated by the disease (Friederici et al., 2003). Furthermore, while the P600 amplitude did not significantly differ as a function of syntactic correctness in PD, early automatic parsing processes (as indexed by the Early Left Anterior Negativity, ELAN) seemed to be largely preserved. These analyses were taken to suggest that syntactic rather than semantic and late integrational rather than early automatic processes are affected by PD. Note, however, that these dissociations are based on the absence of a significant P600 effect in PD, and not on a significant reduction of the P600 effect in PD patients when compared to healthy controls. Future studies involving larger sample sizes are required to establish the absence of P600 effects as a correlate of altered syntactic integration in PD patients and dissociate the influence of PD pathology from the effects of dopaminergic medication on language processing (De Letter et al., 2012).

5.2   Memory

In the section on novelty processing, we have already discussed the observation that PD patients lack the typical von Restorff effect (i.e., better memory for a word when it is written in a novel font), possibly as a result of a failure to allocate attentional resources to the novel information (Schomaker et al., 2014). This finding is compatible with further studies on the ERP correlates of memory processes in PD. Kida et al. (2007) presented patients and healthy controls with a series of unfamiliar faces and contrasted ERPs elicited by the first presentation of a face with the potentials evoked by the same stimulus when it was repeated later in the series. Healthy controls showed an enhanced positive waveform between 300 and 500 ms after stimulus presentation for repeated compared to novel faces. This ERP repetition positivity was absent in patients with PD, which may point to a disease-related deficit in recognition memory. In support

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of this conclusion, response latency and accuracy data collected in this study revealed that PD patients had difficulties judging new stimuli as being new. The same recognition deficit could be found in a similar study using auditory presentation of words (Minamoto et al., 2001). The PD-related memory impairment was accompanied by reduced amplitudes of a negative waveform peaking in the same latency range as the potential analyzed by Kida et al. (2007). Hence, N400-like waveforms appear to reflect altered recognition memory in PD, a conclusion that is further corroborated by a study of Tachibana et al. (1999). Here, in comparison to the first presentation, the second presentation of a word resulted in attenuated N400-like amplitudes in healthy controls, both when the repetition occurred on successive trials and when up to 77 words were interspersed between the first and the second presentation. In PD patients, however, this ERP repetition effect was only present when the word was directly repeated and had already vanished when the repetition occurred after five words. Together, these three studies on ERP waveform modulations in the N400 time range point to a consistent alteration in memory processes in PD, specifically when it comes to the integration of incoming stimulus information with the recent memory context.

In addition, the results presented by Lee et al. (2010) point to a potential deficit in visual working memory in PD patients. In this study, participants were asked to remember the orientation of objects appearing on one side of the screen. After a retention interval of 800 ms, the display was presented again and participants had to indicate whether the objects' orientation had changed. During the retention interval, contralateral delay activity (CDA) was measured as a sustained negativity over posterior electrodes contralateral to the side of stimulus presentation. The CDA amplitude likely reflects the number of items held in working memory (Luria et al., 2016; Vogel and Machizawa, 2004). In contrast to healthy controls, the CDA amplitude was

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attenuated in PD patients, possibly indicating that PD patients have difficulty retaining all relevant information in visual working memory.

5.3   Feedback evaluation in decision-making

Value-based decision-making in PD patients is an interesting issue due to the close link between this cognitive function and dopaminergic brain networks (Rangel et al., 2008). While PD patients have been repeatedly demonstrated to be impaired on tasks that require adaptive decisions among a set of options, this deficit does not seem to be a general one (Ryterska et al., 2013). First, decision-making in PD typically improves when patients are tested off their dopaminergic medication (e.g., Cools et al., 2003). Second, PD does not seem to affect all stages of the decision-making process to the same extent. Efficient decision-making requires, as a first step, the representation and valuation of a set of possible options before the individual has to choose an option based on the assigned values. Then, the outcomes of the chosen action need to be evaluated in order to update value representations for future decisions (Rangel et al., 2008). A recent meta-analysis suggests that PD-related decision-making deficits can largely be attributed to alterations in this latter process of feedback evaluation (Ryterska et al., 2013).

The ERP technique offers some possibilities to further investigate this hypothesis at the cortical level. In a study by Mapelli et al. (2014), for example, ERPs elicited by positive and negative feedback stimuli in a gambling task have been compared between HC and PD patients on medication. In accordance with multiple studies using similar paradigms, negative outcomes evoked a relative fronto-central negativity about 300 ms after stimulus onset in HC. This so-called feedback-related negativity (FRN; Miltner et al., 1997) was absent in the patient group, indicating that neural responses from PD patients failed to distinguish between positive and negative outcomes. This evidence for impaired negative feedback processing in PD may also account for the finding that task performance in this study did not markedly improve over time in

PD patients (Mapelli et al., 2014). In a further study, the PD-related reduction in FRN amplitude was found to be especially pronounced in patients showing elevated levels of apathy (Martínez-Horta et al., 2014).

The PD-related insensitivity to feedback valence does not only become evident after outcome presentation of feedback stimuli, but also in anticipation of these events. The stimulus preceding negativity (SPN) over fronto-central electrode sites is typically enlarged when the occurrence of motivationally significant events can be expected (van Boxtel and Böcker, 2004). This notion could also be supported by Mattox et al. (2006), who found SPN amplitudes to be larger prior to high reward values as compared to low reward values in a sample of HCs. In PD patients, however, this effect was reversed, suggesting severe alterations in anticipation of outcome valence in PD.

Although there is a surprisingly small number of ERP studies on decision-making in PD, these studies paint a consistent picture of PD-related impairment at the stage of outcome evaluation (see also Frank et al., 2004). Future studies need to contrast different stages of the decision-making process and to disentangle effects of the primary disease pathology and dopaminergic medication.

5.4   Emotion

ERP correlates of emotional processing in PD patients were first examined by Wieser et al. (2006) who asked their participants to rate the emotional arousal associated with positive and negative visual stimuli. Compared to healthy controls, PD patients rated highly arousing stimuli as well as pictures of negative valence as less exciting. The early parietal negativity (EPN), an ERP waveform developing 200 ms after stimulus onset, could be demonstrated to vary with emotional arousal, but this potential did not reveal any alteration in the PD group. These results are quite consistent with a study by Dietz et al. (2013), showing that, in the absence of any early

ERP alterations, PD patients rated unpleasant stimuli as less arousing in comparison to pleasant

pictures and in comparison to healthy controls. This finding was accompanied by a selective PD-

related reduction of a late centro-parietal positivity in response to unpleasant words. Interestingly,

this pattern of decreased emotional reactivity to aversive stimulation could be linked to patients'

apathy scores and hence to one of the most prevalent non-motor symptoms in PD (Aarsland et al.,

2007).

When PD patients are explicitly required to discriminate the valence of emotional stimuli,

PD-related differences can also be identified at earlier stages of information processing.

Participants in a more recent study by Wieser et al. (2012) were asked to distinguish different

emotional categories from facial expressions. EPN was found to be enhanced for emotional faces

when compared to neutral faces in healthy controls, but not in patients with PD. However,

emotion recognition rates did not differentiate between the two groups. Auditory ERP paradigms

have also been used to investigate PD patients' perception of emotional speech. By using sadly

spoken and happily spoken target words in an oddball procedure, Schröder et al. (2006) were able

to show that patients had difficulties discriminating emotional prosody. This performance

decrement was also mirrored on the level of the ERPs with decreased P3b amplitude in PD

patients for happy but not for sad targets. A further study by Garrido-Vásquez et al. (2013)

demonstrated that when healthy controls were required to detect different emotions from prosody,

the amplitude of the P2 waveform (Kopp et al., 2007; Kopp and Wessel, 2010) decreases for fear

and disgust prosody compared to neutral prosody. While the same pattern could be observed in

PD patients who showed predominantly right-sided motor symptoms, no disgust effect on P2

amplitude could be observed in patients showing predominantly left-sided motor symptoms.

While providing additional ERP evidence for altered early processes of emotion recognition in

PD, this study also highlights the significance of asymmetric neuronal degeneration for understanding PD-related cognitive changes.

In sum, it appears that ERP correlates of emotional processing in PD are less sensitive to emotional content when patients are explicitly instructed to discriminate emotional content. However, this lack of sensitivity is not consistently associated with poorer emotion recognition performance. Moreover, ERP evidence suggests that PD patients are less aroused by emotional stimuli than healthy controls and future research in this area is needed to establish the role of this phenomenon in understanding PD-related symptoms of apathy and depression.

6   General conclusions, open questions, and directions for future research

We reviewed the available literature investigating cognitive ERPs in PD. The main findings are summarized in Table 6. We found that by-and-large two independent lines of ERP research were pursued in PD. Their results are in general agreement with the 'dual-syndrome hypothesis' of cognitive dysfunction in PD (Kehagia et al., 2013; Robbins and Cools, 2014), and this conclusion constitutes a highlight of the reviewed literature. The 'dual-syndrome hypothesis' defines one cluster of cognitive dysfunction in PD that comprises non-demented PD patients with mild cognitive impairment who primarily show deficits in executive functions. PD-related executive dysfunctions likely reflect fronto-striatal alterations (Dirnberger and Jahanshahi, 2013), and they are sensitive to dopaminergic medication (Kehagia et al., 2013). There is reasonably good evidence for attenuated NoGo-P3 amplitudes in medicated PD patients, and less clear-cut evidence which points to reduction of conflict-N2 amplitudes in individuals at risk for developing PD (as identified by gene mutations associated with PD) as well as in drug-naive, but not in chronically medicated, PD patients. In addition, the reviewed data on consistently attenuated N_e/ERN amplitudes imply that both insufficient and excessive levels of dopamine impair performance monitoring in PD (cf. Fig. 4, left panel).

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The second cluster of PD patients show decline in non-frontal cognitive functions (such as visuospatial abilities, Miller et al., 2013), and the presence of these cognitive dysfunctions during early stages of the disease predicts rapid progression to PDD (Robbins and Cools, 2014; Williams-Gray et al., 2009). PDD is a form of dementia which has been attributed to the degeneration of temporal and parietal cortical areas and the nucleus basalis of Meynert (Gratwicke et al., 2015; Kehagia et al., 2013). We found good evidence for prolonged P3b latencies in PDD, suggesting prolonged duration of stimulus evaluation. We also found a lack of consistent effects of dopaminergic medication on P3b latency prolongation in PDD. Taken together, prolonged P3b latencies in PDD do not seem to result from PD-specific neurodegeneration, i.e., from nigro-striatal dopamine depletion. This conclusion is further corroborated by the fact that P3b latency prolongation is known to occur in other forms of dementia as well, such as for example in AD. Thus, prolonged P3b latency might serve as a biomarker of the presence of dementia in PD, but this lacks nosological specificity. The MMN data are much less clear-cut, but they indicate that the MMN amplitude may be attenuated in PDD in a nosologically specific manner, suggesting specifically disturbed sensory processing in Lewy-body related neurodegeneration. One of the reasons why P3b latency prolongation and MMN amplitude attenuation may differ with regard to their nosological specificity can be sought in the neural origins of these scalp-recorded ERPs: The P3b has its origins in posterior cortical regions, with no contribution from prefrontal regions, whereas the MMN is generated from the auditory cortices bilaterally, but there is an additional contribution from the right lateral prefrontal cortex (see Introduction).

In conclusion, the reviewed research suggests that ERPs might serve as useful biomarkers of different facets of cognitive impairment in PD. Attenuated amplitudes of the NoGo-P3, the conflict-N2, and, most promisingly, the N_e/ERN may indicate changes of executive functioning

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in PD, which possibly relate to early nigro-striatal and later mesocortical dopamine depletion. In contrast, prolonged P3b latencies and attenuated MMN amplitudes appear to be sensitive to the presence of PDD. In search of biomarkers for PDD, previous studies have already demonstrated the usefulness of cerebrospinal fluid levels of amyloid-β and total and phosphorylated tau to discriminate patients with PDD from PD patients without dementia (see Aarsland, 2016; Delgado-Alvarado et al., 2016; Irwin et al., 2013; Svenningsson et al., 2012 for review). In combination with these markers, the electrophysiological indicators identified here could contribute to a multi-modal approach of disease diagnosis and prediction (Aarsland, 2016; Delgado-Alvarado et al., 2016; Svenningsson et al., 2012).

Despite the progress that has been made in the field that we document here for the first time in its entirety (see Růžička and El Massioui, 1993, for an earlier review), many questions remain open for future research. For example, further studies are required to clarify whether ERPs can make useful contributions to the routine assessment of cognitive symptoms. As correlates of cognitive processes, ERPs may mirror more accurately than conventional neuropsychological tests which specific cognitive functions are disturbed in PD and PDD. In this respect, it is important that the ERP technique offers unique solutions to the assessment of cognitive functions, particularly in patients with movement disorders (e.g., Lange et al., 2016a; Rustamov et al., 2013, 2014) or motor neuron disease (e.g., Lange et al., 2016b; Seer et al., 2015), where motor deficits are likely confounding the results of neuropsychological testing. In these disorders, ERPs may also facilitate the monitoring of cognitive change and the evaluation of new treatments for cognitive impairment.

In addition, ERPs might help identify meaningful subgroups of PD patients (e.g., patients with PDD; Luck et al., 2011). A promising approach to this problem is to use ERP data to classify individuals, e.g., as members of a group of patients with a given disease or as members

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of a group without that disease. This technique has been applied to classify patients with schizophrenia with some success, particularly when using multiple paradigms and outcome variables (Laton et al., 2014; Neuhaus et al., 2011).

Finally, ERPs can be even more useful if they predict individual differences in disease progression and/or treatment response. For example, it would be very interesting to know whether P3b latency provides a biomarker predicting – at the earliest stages of the disease – progression to dementia in PD patients at later stages of the disease. Another remarkable possibility is that NoGo-P3, N2, and/or N_e/ERN amplitude measures may serve to titrate the treatment dose of dopaminergic therapy in individual PD patients.

However, there are limitations in the ERP technique as currently applied to the study of PD. These limitations require attention before ERPs can be considered a valuable contribution to care for PD patients. Due to small sample sizes, the statistical power of single studies is in most cases insufficient to detect the effects of interest. Sufficient statistical power and highly reliable results are best ensured by conducting multi-site, large-N studies (e.g., $N > 500$). It has been demonstrated by a number of multi-site, large-N studies in psychiatric research that the technique ERP is feasible for these types of studies (e.g., Hesselbrock et al., 2001; Light et al., 2015; Olincy et al., 2010; Turetsky et al., 2015; see also Luck et al., 2011). An essential prerequisite for conducting multi-site, large-N studies is to standardize assessment protocols adequately. To date, studies vary widely with regard to stimulus materials, recording procedures, response modes, and analysis methods. Standardized assessment protocols would not only be required for the conductance of multi-site, large-N studies; they are also a prerequisite for implementing ERPs in clinical practice. The assessment of sensory evoked potentials, which are used as objective measures of sensory function in clinical practice, may serve as an example of a successful clinical implementation of the ERP technique (Chiappa, 1997; Duncan et al., 2009).

The majority of previous ERP studies in PD relied on simple group comparisons between small groups of PD patients and matched controls, often aiming to investigate whether a particular ERP waveform is 'normal' or altered in PD. To benefit from the potential of ERPs as diagnostic tools, it is necessary to address more refined questions, such as whether ERPs are more state-like (i.e., sensitive for intra-individual fluctuations) or more trait-like (i.e., stable across intra-individual fluctuations) biomarkers of cognitive impairment in PD (Luck et al., 2011). The evidence to date suggests that prolonged P3b latencies should be considered as a trait-like marker of cognitive decline to dementia in PD, found to be largely independent of dopaminergic fluctuations. However, it still remains to be delineated to what degree NoGo-P3, N2, and/or N_e/ERN amplitude attenuation in PD are sensitive to dopaminergic fluctuations, i.e., to the depletion of dopamine in PD and to its substitution by dopaminergic therapy. Intra-individual (within-subjects) designs investigating the impact of different types and doses of dopaminergic medication may help clarify the relationship between dopamine and ERPs of executive processes in PD. These studies should preferably be conducted in a placebo-controlled and counterbalanced way to eliminate some of the confounding factors in previous medication studies on the ERP correlates of PD. Fig. 4 (right panel) shows testable predictions for intra-individual designs which can be derived from the reviewed data.

Advances in surgical treatment of PD, namely DBS, facilitate investigating the neuroanatomical basis of ERPs measured in patients with PD. Similar to intra-individual comparisons of dopaminergic medication states as proposed above, within-subjects comparisons can be performed on and off stimulation states (e.g., Gerschlager et al., 2001). Such studies may help to reveal the role of the stimulated basal ganglia nuclei for specific cognitive processes and their ERP correlates. In addition, DBS allows for electrophysiological recordings directly from the stimulated site (i.e., the recording of local field potentials; e.g., Siegert et al., 2014) and thus

provides the possibility to examine electrophysiological correlates of cognitive processes at the level of neuronal populations (Münte et al., 2008).

In conclusion, we think that the progress that has been made in the reviewed field represents a currently widely underrecognized scientific achievement. Based on quality-assured (Luck et al., 2011) and source-resolved (Light and Makeig, 2015) ERP measures, the pursuance of multi-site, large-N studies as well as of longitudinal studies will move the field one step forward toward the clinical utility and application of ERPs in PD.

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Table 1

Overview of the studies assessing P3b measures using oddball paradigms in patients with Parkinson's disease.

| Study | N | | | | | | | oddball | stimulus | % | response | P3b | |
	PD	HC	med	HY	age	dur	dem	task	modality	target	mode	latency	amplitude
Antal et al. (1996)*	20	20	on	1.9	63.2	6.7	no	2stim	vis	mix	press	→	↓
Antal et al. (2000)	20	20	on	2.3	65.3	4.8	no	2stim	vis	20	press	↑	↓
Aotsuka et al. (1996)	21	-	-	-	-	-	no	2stim	aud	20	-	↑	↓
Bathien et al. (1996) cognitively unimpaired	15	10	-	2.1	64.5	10.0	no	2stim	vis	20	press	→	→
Bathien et al. (1996) cognitively impaired	10	10	-	3.1	70.6	13.8	no	2stim	vis	20	press	↑	→
Bocquillon et al. (2012)	15	15	on	1.5	59.2	4.8	no	3stim	vis	8	press	↑	→
Chen et al. (2006)	27	27	on	-	63.3	40.1	no	2stim	aud	15.4	press	→	→
Chia et al. (1995)	22	16	on	2.4	67.2	7.4	mix	2stim	aud	15	recognize	↑	-
Ebmeier et al. (1992)*	16	16	on	2.4	69.0	9.3	no	2stim	aud	12.5	mix	→	-
Elwan et al. (1996)	43	37	off	2.6	61.8	2.4	mix	2stim	aud	30	press	↑	-
Fogelson et al. (2011)	8	8	on	2.3	61.6	6.8	no	2stim	vis	15	press	↓	↑
Gaudreault et al. (2013)	15	16	on	2.2	63.1	5.4	no	3stim	vis	15	press	→	→
Georgiev et al. (2015)	14	13	on/ off	1.8	60.4	3.5	no	3stim	mix	15	count	→	→

Study													
Gerschlager et al. (2001)	8	8	off	-	66.9	14.5	no	2stim	aud	20	press	↑	→
Gil et al. (1989)	24	24	mix	-	63.8	4.6	mix	2stim	aud	33	count	↑	↓
Goodin & Aminoff (1987) dem	14	40	on	2.5	71.4	4.8	yes	2stim	aud	14	count	↑	-
Goodin & Aminoff (1987) non-dem	14	40	on	2.7	67.2	5.0	no	2stim	aud	14	count	→	-
Graham et al. (1990)	-	-	off	-	-	-	no	2stim	aud	-	press	→	→
Green et al. (1996)	20	20	off	1.3	54.1	-	no	2stim	aud	14	press	→	↑
Hanafusa et al. (1991)	8	29	-	-	74.5	-	yes	2stim	aud	20	press	↑	-
Hansch et al. (1982)	20	20	on	-	64.3	10.2	mix	2stim	aud	15	count	↑	→
Hautecœur et al. (1991) dem	28	20	-	2.3	72.4	3.3	yes	2stim	aud	15	count	↑	↓
Hautecœur et al. (1991) non-dem	55	20	-	2.0	69.0	3.1	no	2stim	aud	15	count	→	→
Hayashi et al. (1993)	53	-	-	-	-	-	-	2stim	-	-	press	↑	-
Hayashi et al. (1996) HY stage 2	11	12	on	2.0	54.4	5.4	mix	2stim	aud	20	count	→	-
Hayashi et al. (1996) HY stage 3	18	13	on	3.0	60.8	6.0	mix	2stim	aud	20	count	↑	-
Hozumi et al. (2000)	15	13	on	2.1	65.4	5.6	no	3stim	aud	20	count	→	→
Iijima et al. (2000)	20	55	on	2.2	63.1	4.9	no	2stim	aud	20	count	↑	→

Study													
Ito (1994) dem	13	18	on	-	66.0	-	yes	2stim	som	20	count	↑	→
Ito (1994) non-dem	11	18	on	-	65.0	-	no	2stim	som	20	count	→	→
Jiang et al. (2000)	12	9	on	2-3	66.3	6.3	no	2stim	aud	20	count	↑	↓
Karayanidis et al. (1995)	16	15	on	1-2	67.2	3.0	no	2stim	aud	7	press	→	→
Katsarou et al. (2004)	45	40	on	2-3	59.3	6.1	no	2stim	aud	20	count	↑	→
Kim et al. (1995)	16	15	off	2.1	62.6	2.3	no	2stim	aud	-	count	↑	-
Kurita et al. (2010)*	17	20	on	3.7	73.9	9.2	yes	2stim	mix	20	count	↑	-
Lagopoulos et al. (1998b)	15	15	mix	1-3	60.1	5.1	no	2stim	aud	15	press	→	→
Lagopoulos et al. (1998a)	15	50	-	-	-	-	no	2stim	aud	-	press	↑	→
Li et al. (2005)	22	23	on	2.6	64.2	6.3	-	3stim	vis	20	press	↑	↓
Lopes et al. (2014)	43	33	on	2.3	63.1	7.0	mix	2stim	aud	20	count	↑	-
Lukhanina et al. (2009)	61	21	off	2.4	61.4	7.6	mix	2stim	aud	22.5	count	↑	→
Lukhanina et al. (2008)	35	18	-	1.5-3	61.1	4.5	mix	2stim	aud	20	count	↑	→
Morita et al. (2005)	18	18	-	3.5	67.3	9.9	no	2stim	vis	20	mix	↑	→
Nojszewska et al. (2009)	42	14	on	2.5	65.8	7.8	no	2stim	aud	20	count	→	-
Oishi et al. (1996)	10	10	off	2-3	63.0	-	no	2stim	aud	20	count	↑	→
O'Donnell et al. (1987)	16	11	on	2.6	65.8	6.3	mix	2stim	aud	15	count	↑	-

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Philipova et al. (1997)	17	17	on	-	54.0	2.9	no	2stim	aud	60	count	→	↓
Pirtošek et al. (2001)	19	8	off	2.5	67.0	3.0	no	3stim	aud	15	press	→	→
Potagas et al. (2003)	53	20	on	2.5	67.7	7.8	no	2stim	vis	20	press	↑	↑
Prabhakar et al. (2000)	25	25	off	-	58.2	1.8	no	2stim	aud	-	count	→	-
Prasher & Findley (1991)	27	27	off	1-2	56.0	2.0	mix	2stim	aud	30	press	→	-
Raudino et al. (1997)	49	39	on	-	65.7	4.9	mix	2stim	aud	20	count	→	↓
Rumbach et al. (1993)	26	32	on	2.2	66.0	4.2	mix	2stim	aud	20	press	↑	→
Růžička et al. (1994)	8	9	off	2.5	59.4	8.3	no	2stim	aud	20	count	→	→
Sagliocco et al. (1997)	17	17	on	2.1	61.9	31.3	no	2stim	vis	20	count	→	→
Sarikaya et al. (2014)	38	39	on	1.9	58.8	5.8	no	2stim	aud	20	count	↑	→
Sartucci et al. (1990)	21	13	mix	2.4	61.8	6.9	mix	2stim	aud	25	count	→	→
Smolnik et al. (2002)	13	13	off	-	67.0	8.4	no	2stim	aud	20	press	→	→
Sohn et al. (1998) off	19	13	off	2.1	64.0	2.3	no	2stim	aud	-	count	↑	-
Sohn et al. (1998) on	18	13	on	2.6	61.0	3.6	no	2stim	aud	-	count	↑	-
Stamenović et al. (2005)	30	15	off	1.4	61.3	-	no	2stim	aud	-	count	↑	-
Stanzione et al. (1991)	18	20	off	2.3	64.9	3.0	no	2stim	aud	20	count	↑	-
Stanzione et al. (1998)	44	31	off	2.1	60.7	2.3	no	2stim	aud	20	count	→	→

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Study	PD	HC	med	HY	age	dur	dem	task	mod		resp		
Tachibana et al. (1992) dem	6	37	on	3.0	70.7	5.4	yes	3stim	vis	19	press	↑	→
Tachibana et al. (1992) non-dem	25	37	on	2.3	66.0	2.7	no	3stim	vis	19	press	→	→
Tachibana et al. (1997)	29	19	mix	2.4	63.9	6.0	no	2stim	vis	20	press	↑	→
Tanaka et al. (2000) dem	7	11	on	3.3	64.1	7.7	yes	2stim	aud	20	count	↑	→
Tanaka et al. (2000) non-dem	15	11	on	2.4	64.1	5.6	no	2stim	aud	20	count	→	↑
Toda et al. (1993) dem	9	15	on	2.4	67.9	-	yes	3stim	vis	19	press	↑	→
Toda et al. (1993) non-dem	26	15	on	2.4	67.2	-	no	3stim	vis	19	press	→	→
Tsuchiya et al. (2000)	18	35	on	2.2	64.4	5.5	no	3stim	aud	20	press	→	↓
Vieregge et al. (1994)	14	16	on	2.2	61.0	5.0	no	2stim	aud	14	press	→	→
Wang et al. (1999)	38	24	on	2.5	65.8	7.4	no	3stim	vis	20	press	→	→
Wright et al. (1996)*	17	28	mix	2.0	62.5	6.8	no	2stim	aud	25	mix	→	→
Zeng et al. (2002)*	18	16	on	1.7	63.9	4.6	no	mix	mix	20	press	→	↑

Note. For studies reporting a within-subject manipulation of task parameters (e.g., visual vs. auditory; on vs. off medication), P3b results were evaluated based on the mean across different conditions. These studies are marked with an asterisk (*) in the table.
2stim = two-stimulus oddball task; 3stim = three-stimulus oddball task; aud = auditory; dem = demented; dur = disease duration in years; HC = healthy controls; HY = mean score obtained on the Hoehn & Yahr scale; med = antiparkinsonian medication state; mix = mixed; non-dem = non-demented; PD = patients with Parkinson's disease; vis = visual; ↑ indicates larger values of the respective measure in PD;

↓ indicates smaller values of the respective measure in PD; → indicates that no significant difference was found in the respective measure between PD and HC; - indicates that the measure could not be extracted from the respective study, either because it was not reported, or because the full version of the article could not be accessed.

Table 2

Overview of the studies investigating novelty processing and deviance detection in patients with Parkinson's disease.

Study	N PD	HC	med	HY	age	dur	dem	stim mod	% tar	% distr	task dim	distr type	resp mode	P3a three-stimulus oddball task latency	amplitude
Bocquillon et al. (2012)	15	15	on	1.5	59.2	4.8	no	vis	8	8	size	dev shape	press	→	→
Gaudreault et al. (2013)	15	16	on	2.2	63.1	5.4	no	vis	15	15	pos	novel shape	press	→	→
Georgiev et al. (2015) on | aud	14	13	on	1.8	60.4	3.5	no	aud	15	15	freq	noise	count	→	→
Georgiev et al. (2015) on | vis	14	13	on	1.8	60.4	3.5	no	vis	15	15	size	dev shape	count	→	→
Georgiev et al. (2015) off | aud	14	13	off	1.8	60.4	3.5	no	aud	15	15	freq	noise	count	→	→
Georgiev et al. (2015) off | vis	14	13	off	1.8	60.4	3.5	no	vis	15	15	size	dev shape	count	→	→

Study															
Hozumi et al. (2000)	15	13	on	2.1	65.4	5.6	no	aud	20	10	freq	dev freq	count	↓	→
Li et al. (2005)	22	23	on	2.6	64.2	6.3	-	vis	20	20	shape	dev shape	press	→	↓
Pirtošek et al. (2001)	19	8	off	2.5	67	3	no	aud	15	15	freq	dev freq	press	→	→
Tachibana et al. (1992) non-dem	25	37	on	2.3	66	2.7	no	vis	19	19	shape	dev shape	press	→	→
Tachibana et al. (1992) dem	6	37	on	3	70.7	5.4	yes	vis	19	19	shape	dev shape	press	→	→
Toda et al. (1993) non-dem	26	15	on	2.4	67.2	-	no	vis	19	19	shape	dev shape	press	→	→
Toda et al. (1993) dem	9	15	on	2.4	67.9	-	yes	vis	19	19	shape	dev shape	press	→	→
Tsuchiya et al. (2000)	18	35	on	2.2	64.4	5.5	no	aud	20	15	freq	novel sound	press	↑	↓
Wang et al. (1999)	38	24	on	2.5	65.8	7.4	no	vis	20	20	shape	dev shape	press	→	↓
Wang et al. (2000)	16	22	on	1.9	62.5	2.3	no	vis	20	20	shape	dev shape	press	→	↓

														P3a distraction paradigm	
														latency	amplitude
Zeng et al. (2002) aud	18	16	on	1.7	63.9	4.6	no	aud	20	16	words	novel noise	press	↑	→
Zeng et al. (2002) vis	18	16	on	1.7	63.9	4.6	no	vis	20	16	words	novel figure	press	↑	→
Solís-Vivanco et al. (2011) on	25	20	on	-	55.1	4.9	no	aud	50	10	durat	dev freq	press	→	↓
Solís-Vivanco et al. (2011) off	17	20	off	-	56.9	2.4	no	aud	50	10	durat	dev freq	press	→	↓
Solís-Vivanco et al. (2015) HY stage 1	28	24	mix	1	56.2	3	no	aud	50	10	durat	dev freq	press	→	→
Solís-Vivanco et al. (2015) HY stage 2	14	24	mix	2	57.2	5.3	no	aud	50	10	durat	dev freq	press	→	↓

Study	n1	n2	med	dur	age	sd	dem	mod	relev	irrelev	relev type	irrelev type	task	latency	amplitude
Solís-Vivanco et al. (2015) HY stage 3	13	24	on	3	64.9	10	no	aud	50	10	durat	dev freq	press	→	↓

												MMN irrelevant oddball sequence			
														latency	amplitude
Brønnick et al. (2010) non-dem	16	18	on	2	69.3	5.6	no	aud	-	10	-	dev durat	-	→	→
Brønnick et al. (2010) dem	15	18	on	3.2	72.7	2.2	yes	aud	-	10	-	dev durat	-	→	↓
Karayanidis et al. (1995)	16	15	on	1-2	67.2	3.0	no	aud	7	7	durat relev ear	dev durat irrelev ear	press	→	→
Pekkonen et al. (1995)	13	11	on	1.2	64	3.5	no	aud	-	15	-	dev freq	-	-	↓
Pekkonen et al. (2000)	16	11	-	1	-	-	no	aud	-	-	-	dev durat	-	→	→
Vieregge et al. (1994)	14	16	mix	2.3	61	5	no	aud	10	10	durat relev ear	dev durat irrelev ear	press	→	→

														MMN	

													distraction paradigm	
													latency	amplitude
Solís-Vivanco et al. (2011) on	25	20	on	-	55.1	4.9	no	aud	50	10	durat	dev freq	press	→	→
Solís-Vivanco et al. (2011) off	17	20	off	-	56.9	2.4	no	aud	50	10	durat	dev freq	press	→	→
Solís-Vivanco et al. (2015) HY stage 1	28	24	mix	1	56.2	3	no	aud	50	10	durat	dev freq	press	→	→
Solís-Vivanco et al. (2015) HY stage 2	14	24	mix	2	57.2	5.3	no	aud	50	10	durat	dev freq	press	→	→
Solís-Vivanco et al. (2015) HY stage 3	13	24	on	3	64.9	10	no	aud	50	10	durat	dev freq	press	→	→
													RON distraction paradigm	
													latency	amplitude

Study															
Solís-Vivanco et al. (2011) on	25	20	on	-	55.1	4.9	no	aud	50	10	durat	dev freq	press	→	→
Solís-Vivanco et al. (2011) off	17	20	off	-	56.9	2.4	no	aud	50	10	durat	dev freq	press	→	↓
Solís-Vivanco et al. (2015) HY stage 1	28	24	mix	1	56.2	3	no	aud	50	10	durat	dev freq	press	→	→
Solís-Vivanco et al. (2015) HY stage 2	14	24	mix	2	57.2	5.3	no	aud	50	10	durat	dev freq	press	→	→
Solís-Vivanco et al. (2015) HY stage 3	13	24	on	3	64.9	10	no	aud	50	10	durat	dev freq	press	→	→

Note. aud = auditory; dem = demented; dev = deviant; distr = distractor; dur = disease duration in years; durat = duration; freq = frequency; HC = healthy controls; HY = mean score obtained on the Hoehn & Yahr scale; irrelev = irrelevant; med = antiparkinsonian medication state; mix = mixed; MMN = mismatch negativity; non-dem = non-demented; PD = patients with Parkinson's disease; pos = position; relev = relevant; resp mode = response mode; RON = reorienting negativity; stim mod = stimulus modality; tar = target; task dim = task-relevant dimension; vis = visual; ↑ indicates larger values of the respective measure in PD; ↓ indicates smaller values of the respective measure in PD; → indicates that no significant difference was found in the respective measure between PD and HC; - indicates that the measure could not be extracted from the respective study.

Table 3

Overview of the studies investigating N2 and P3 measures using Go/NoGo tasks in patients with Parkinson's disease.

Study	PD	HC	med	HY	UPDRS	age	dur	dem	trial type	N2 latency	N2 amplitude	P3 latency	P3 amplitude
Beste et al. (2009a)[a]	15	15	on	-	-	61.1	-	no	all trials	↑	↑	→	↓
									Go	-	→	-	→
									NoGo	-	↑	-	↓
									NoGo − Go	→	-	comp: → incomp: ↑	-
Beste et al. (2010)	18	18	off	-	14.6	60.5	-	no	all trials	-	↑	→	→
									NoGo − Go	-	→	-	→
Bokura et al. (2005)	13	14	on	2.9	-	71[b]	7.2	no	Go	-	-	→	→
									NoGo	-	-	↑	↓
									NoGo − Go	→	↓	-	-
Osawa et al. (2005)	17	17	mix	2.1	-	66.4	4.1	mix	NoGo[c]	-	→	-	↓
Pulvermüller et al. (1996)	18	14	on	2.2	-	60.6	8.3	no	all trials	-	-	-	↓
									Go	-	-	-	↓
									NoGo	-	-	-	↓

Note. dem = demented; dur = disease duration in years; HC = healthy controls; HY = mean score obtained on the Hoehn & Yahr scale; med = antiparkinsonian medication state; mix = mixed; PD = patients with Parkinson's disease; UPDRS = mean score obtained on Part III of the Unified Parkinson's Disease Rating Scale; all trials = main effect of group (PD vs HC) obtained irrespective of the Go/NoGo condition; Go = group effect observed on Go-trials; NoGo = group effect observed on NoGo-trials; NoGo − Go = group effect observed on NoGo-minus-Go trials; ↑ indicates larger values of the respective measure in PD; ↓ indicates smaller values of the respective measure in PD; → indicates that no significant difference was found in the respective measure between PD and HC; - indicates that the measure could not be extracted from the respective study.
[a]Beste et al. (2009a) used two versions of the Go/NoGo task where imperative stimuli were either semantically compatible (comp; i.e. Go: 'PRESS', NoGo: 'STOP') or incompatible (incomp; i.e. Go: 'STOP', NoGo: 'PRESS') with the task, respectively.
[b]According to the text in Bokura et al. (2005).

[c]According to Osawa et al. (2005), "the amplitude of nogo N2 trended to be higher (p=0.08) in PD" (p. 342), but it remains unclear whether N2 amplitudes tended to be enhanced (i.e., numerically more negative) or attenuated (i.e., numerically more positive) in PD patients.

Table 4

Overview of the studies investigating N2 and P3 measures using interference tasks in patients with Parkinson's disease.

Study	N PD	HC	HY	UPDRS	age	dur	dem	task	N2 latency	N2 amplitude	P3 latency	P3 amplitude
on antiparkinsonian medication												
Rustamov et al. (2013)	20	20	2.0	15.1	59.0	5.4	no	flanker	incong: → CSE: →	CE: → CSE: ↓	-	-
Stemmer et al. (2007) on medication	9	14	2.6	21.3	63.4	6.7	-	flanker	-	cong: →	-	cong: →
Verleger et al. (2010) on medication	12	13	2.1	19.3	64.9	4.1	no	flanker	-	incong: →	-	-
Willemssen et al. (2011) on medication	20	32	-	10.8	64.5	3.2	-	flanker	→	→	→	→
Willemssen et al. (2011) de novo | post medication	15	32	-	8.7	59.6	-	-	flanker	→	→ CE: →	→	→
off antiparkinsonian medication												
Praamstra & Plat (2001)	8	8	2.4	37.3	57.8	5.8	-	Simon	-	→ – ↓	-	-
Praamstra et al. (1998)	7	7	2.4	31.0	58.4	5.4	-	flanker	→	→	→	→
Willemssen et al. (2011) off medication	20	32	-	14.8	64.5	3.2	-	flanker	→	→	→	→

drug-naive

Stemmer et al. (2007) de novo	9	14	2.1	22.7	64.2	2.2	-	flanker	-	cong: →	-	cong: →
Verleger et al. (2010) mutation carriers	19	13	0.5	-	41	-	no	flanker	-	incong: ↓	-	-
Willemssen et al. (2011) de novo | pre medication	15	32	-	12.7	59.6	-	-	flanker	→	→ CE: ↓	→	→

Note. CE = congruency effect; cong = congruent trials; CSE = congruency sequence effect; dem = demented; dur = disease duration in years; HC = healthy controls; HY = mean score obtained on the Hoehn & Yahr scale; incong = incongruent trials; PD = patients with Parkinson's disease; UPDRS = mean score obtained on Part III of the Unified Parkinson's Disease Rating Scale; ↓ indicates smaller values of the respective measure in PD; → indicates that no significant difference was found in the respective measure between PD and HC; → – ↓ indicates that multiple analyses were reported, yielding either no significant difference (→) or smaller values of the respective measure in PD (↓); - indicates that the measure could not be extracted from the respective study.

Table 5

Overview of the studies investigating electrophysiological measures of performance monitoring in patients with Parkinson's disease.

Study	N								N_e/ERN		N_c/CRN	
	PD	HC	HY	UPDRS	age	dur	dem	task	latency	amplitude	latency	amplitude
on antiparkinsonian medication												
Falkenstein et al. (2001)	13	13	-	25	61.1	-	no	flanker	→	↓	→	→
Falkenstein et al. (2001)	13	13	-	25	61.1	-	no	Simon	↓	↓	→	→
Falkenstein et al. (2001)	14	14	-	25	61.1	-	no	Go/NoGo	→	↓	→	→
Ito & Kitagawa (2006)	17	15	2.1	-	64.1	6.1	no	lexical decision	→	↓	→	→
Rustamov et al. (2014)	20	20	2.1	15.9	59.8	5.7	no	flanker	-	↓	-	-
Stemmer et al. (2007) on	9	14	2.6	21.3	63.4	6.7	-	flanker	-	↓	-	-
Verleger et al. (2013)	12	12	2.1	19.3	64.9	4.1	no	flanker	→	→	-	-
off antiparkinsonian medication												
Beste et al. (2009b) off	17	17	-	15.9	66.8	-	-	flanker	→	↓	→	→
Holroyd et al. (2002)	9	9	2.5	26.9	56.1	6.1	no	flanker	-	→	-	-
Willemssen et al. (2008)	18	18	-	14.8	66.3	3.2	-	flanker	-	↓	-	→
drug-naive												

Beste et al. (2009b) de novo	15	17	-	12.6	59.6	-	-	flanker	→	↓	→	→
Stemmer et al. (2007) de novo	9	14	2.1	22.7	64.2	2.2	-	flanker	-	↓	-	-
Willemssen et al. (2009)	14	14	-	12.5	59.6[a]	-	-	flanker	→	↓	→	↑

Note. dem = demented; dur = disease duration in years; HC = healthy controls; HY = mean score obtained on the Hoehn & Yahr scale; med = antiparkinsonian medication state; N_c/CRN = correct(-related) negativity; N_e/ERN = error(-related) negativity; PD = patients with Parkinson's disease; UPDRS = mean score obtained on Part III of the Unified Parkinson's Disease Rating Scale; ↑ indicates larger values of the respective measure in PD; ↓ indicates smaller values of the respective measure in PD; → indicates that no significant difference was found in the respective measure between PD and HC; - indicates that the measure could not be extracted from the respective study.
[a]According to the text in Willemssen et al. (2009).

Table 6

Overview of the main findings on cognitive ERPs in PD.

ERP	PD-related changes in comparison to healthy controls
Classical cognitive ERPs	
P3b	good evidence for a sensitivity of P3b latency to PDD, with prolongation in demented, but not in non-demented PD patients
P3a	preliminary evidence for a relation of P3a amplitude attenuation to disease duration in PD
mismatch negativity (MMN)	preliminary evidence for a sensitivity of MMN amplitude to PDD, with attenuation in demented, but not in non-demented PD patients
Cognitive ERP correlates of executive control	
(conflict-)N2	preliminary evidence for attenuation of N2 amplitudes in drug-naive PD patients and in pre-symptomatic mutation carriers
	preliminary evidence for attenuation of the contextual modulation of conflict-N2 amplitude in PD patients
NoGo-P3	preliminary evidence for Nogo-P3 amplitude attenuation in (medicated) PD patients
error(-related) negativity (N$_e$/ERN)	good evidence for N$_e$/ERN amplitude attenuation in PD patients

Note. PDD = Parkinson's disease dementia; PD = Parkinson's disease

Figure captions

Fig. 1. Standard paradigms for recording of event-related potentials. In the two-stimulus oddball task depicted here, participants have to respond to rare target stimuli (large circles) embedded in a series of frequent standard stimuli (small circles). In the three-stimulus oddball task, infrequent novel or complex stimuli (deviant shapes) are added to the oddball series. The Go/NoGo task requires participants to respond on Go-trials (e.g., green circles) while withholding responses on NoGo-trials (e.g., red circles). In the flanker task, the participant is required to respond to a central target stimulus which is flanked by either congruent or incongruent distractor stimuli.

Fig. 2. Predictors of P3b latency prolongation in PD patients. Depicted is the proportion of studies that reported significantly prolonged P3b latencies in PD patients (when compared to healthy controls) as a function of sample and task characteristics. p-values are the result of chi-square tests for independence.

Fig. 3. Graphical summary of the key results of this review. Left: The latency of the P3b waveform, elicited by rare target stimuli, has been found to be prolonged in patients with Parkinson's disease (PD) dementia, but not in non-demented PD patients. Right: ERP markers of executive functioning (including the error(-related) negativity, N_e/ERN) have been shown to be altered in non-demented PD patients. Here, the amplitude of the N_e/ERN, elicited by erroneous responses, is attenuated in PD patients compared to healthy controls.

Fig. 4. A. An illustration of the hypothesized inverted U-shaped relationship between dopamine levels (major effect of disease: severe dopamine depletion in the dorsal striatum; proposed effect of dopaminergic treatment: dopamine overdosing in the ventral striatum and/or the prefrontal cortex) and absolute values of ERP amplitudes. Table 3 shows that the NoGo-P3 data are compatible with optimal (i.e., corresponding – by definition – to those of age-stratified healthy

controls) amplitude values in PD patients who are off dopaminergic medication (one study) and

attenuated amplitude values in PD patients who are on dopaminergic medication (four studies;

shown in red). Table 5 shows that several N_e/ERN studies in PD patients yielded attenuated

N_e/ERN amplitudes in PD patients who are off dopaminergic medication (two out of three

studies) as well as attenuated amplitude values in PD patients who are on dopaminergic

medication (six out of seven studies; shown in blue). B. The reviewed evidence leads to testable

predictions for intra-individual ERP studies. Specifically, NoGo-P3 data in PD patients who are

off dopaminergic medication should show amplitude values similar to those of healthy controls

(i.e., age-stratified optimal values) and attenuated amplitude values in these PD patients when

they are on dopaminergic medication (shown in red). Attenuated N_e/ERN amplitudes are

expected in PD patients irrespective of dopaminergic medication (shown in blue).
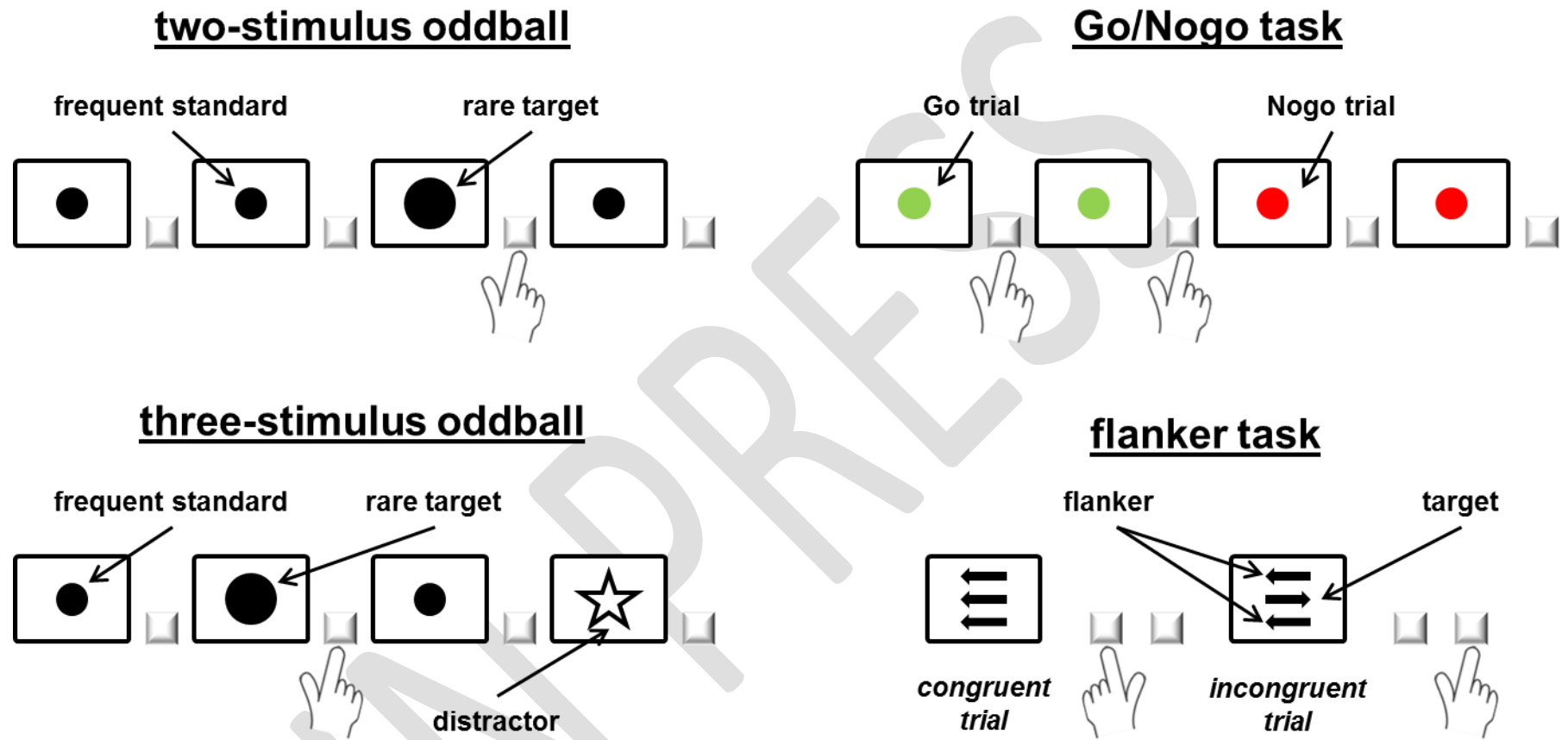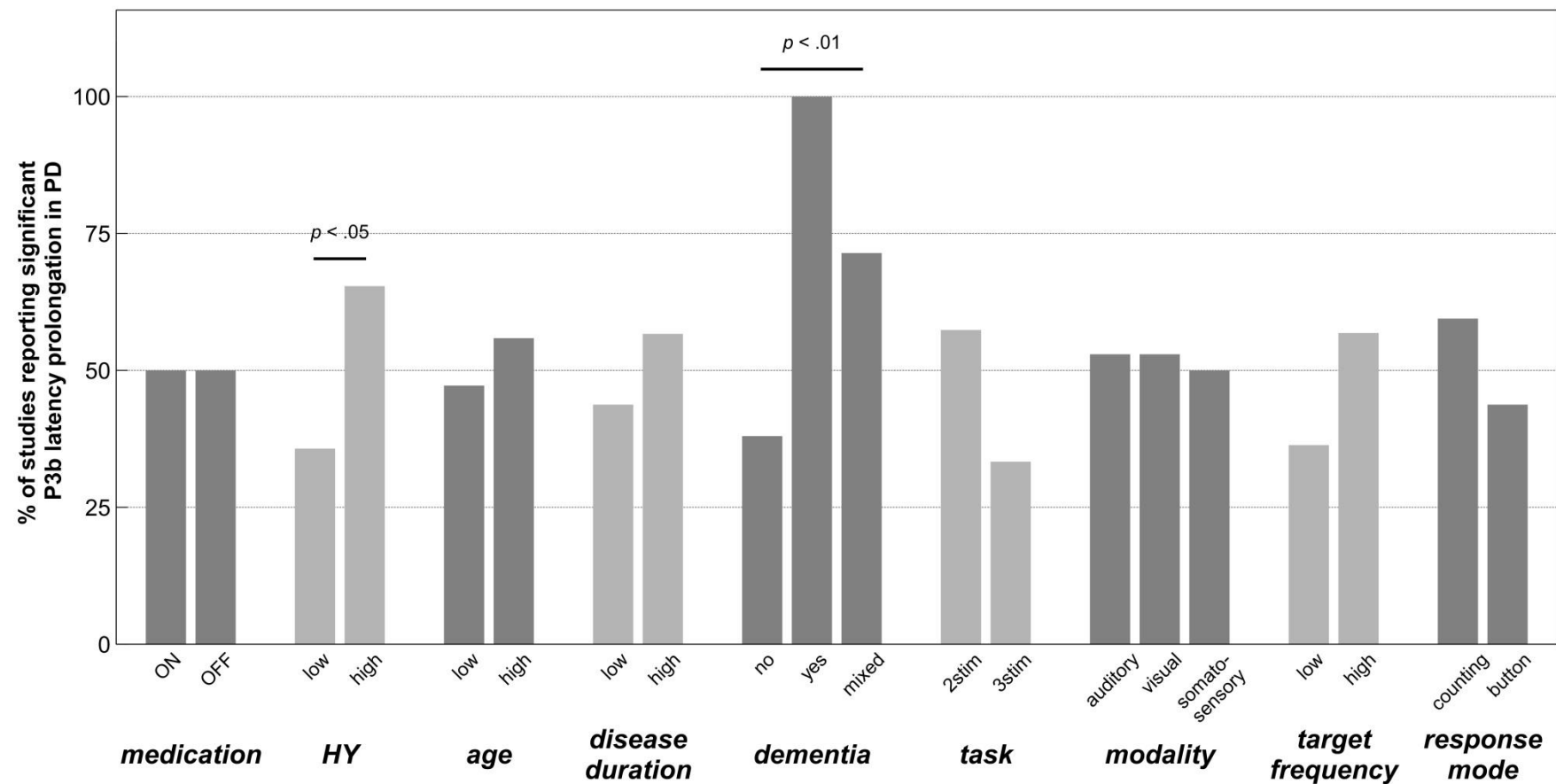
Fig. 1.

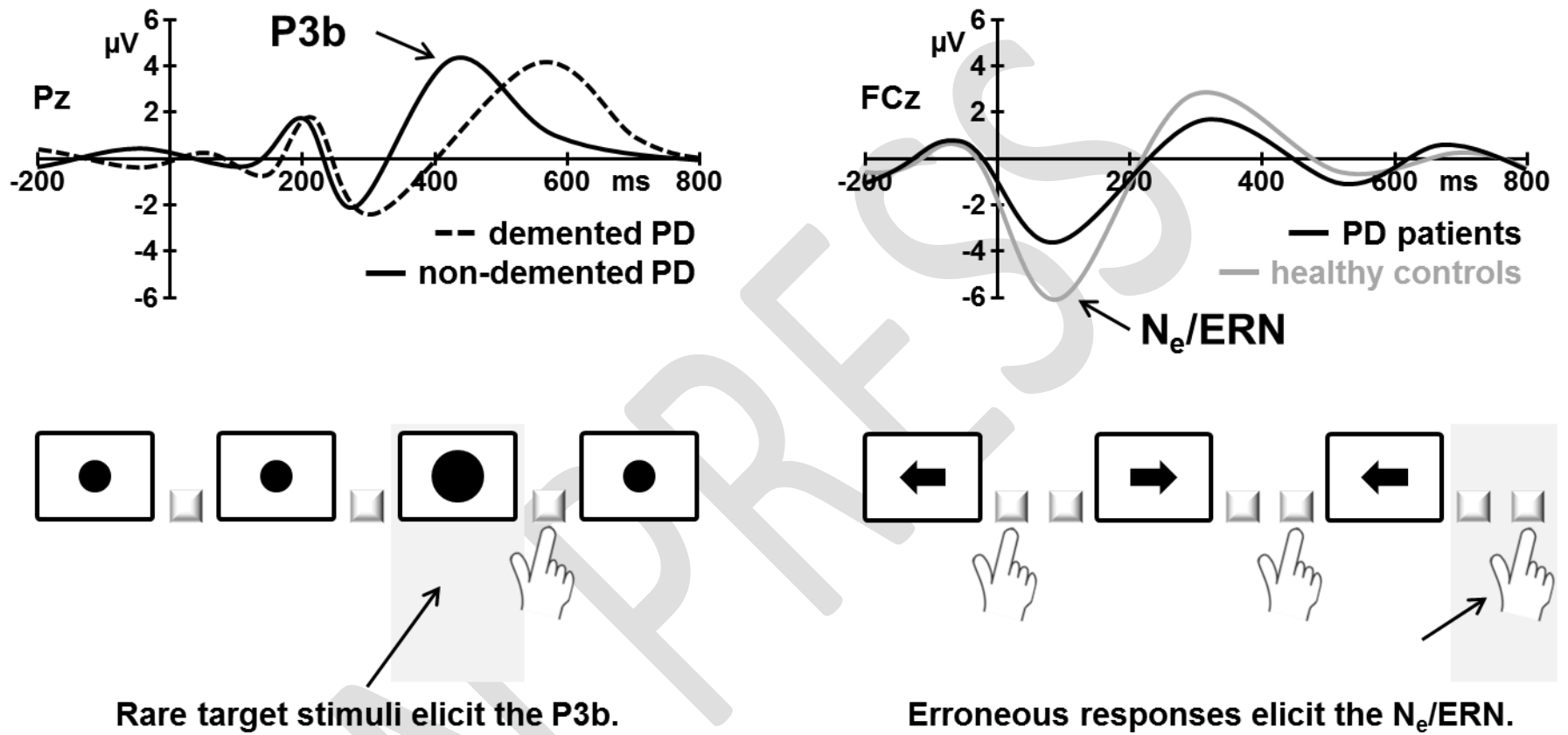**two-stimulus oddball**

frequent standard   rare target

Go/Nogo task

Go trial   Nogo trial

three-stimulus oddball

frequent standard   rare target

distractor

flanker task

flanker   target

congruent trial   *incongruent trial*

Fig. 2.

Fig. 3.

Rare target stimuli elicit the P3b.

Erroneous responses elicit the N$_e$/ERN.

Fig. 4.