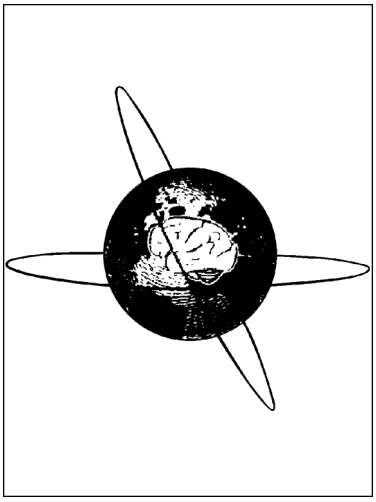

Review

Movement-related potentials in Parkinson's disease

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Movement-related potentials in Parkinson's disease

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Highlights

- We review the literature on movement-related potentials - the BP, the CNV and the LRP, in PD.
- There is clear evidence that the early BP and CNV are affected in dopamine-dependent manner in PD.
- LRP studies suggest impairment of motor control processes relating to the late preparation in PD.

Abstract

To date, many different approaches have been used to study the impairment of motor function in Parkinson's disease (PD). Event-related potentials (ERPs) are averaged amplitude fluctuations of the ongoing EEG activity that are time locked to specific sensory, motor or cognitive events, and as such can be used to study different brain processes with an excellent temporal resolution. Movement-related potentials (MRPs) are ERPs associated with processes of voluntary movement preparation and execution in different paradigms. In this review we concentrate on MRPs in PD. We review studies recording the Bereitschaftspotential, the Contingent Negative Variation, and the Lateralized Readiness Potential in PD to highlight the contributions they have made to further understanding motor deficits in PD. Possible directions for future research are also discussed.

Keywords: Movement-related potentials, Bereitschaftspotential, Contingent Negative Variation, Lateralized Readiness Potential, Parkinson's disease.

Abbreviations

BP = Bereitschaftspotential; CNV = Contingent Negative Variation; CRT = Choice Reaction Task; DBS = Deep Brain Stimulation; DT = dopaminergic therapy; EEG = electroencephalography; ER = Error Rate; ERP = Event-related potential; GPi = globus pallidus pars interna; LRP = Lateralized Readiness Potential; M1 = Primary Motor Cortex; MEG = magnetoencephalography; MP = motor potential; MRP = Movement-related potential; NFB = neurofeedback; NS = Negative Slope; PD = Parkinson's disease; PMP = premotor positivity; PSP = Progressive Supranuclear Palsy; RT = Reaction Time; SMA = supplementary motor area; SNPc = substantia nigra pars compacta; SRT = Simple Reaction Time Task; SPN = Stimulus Preceding Negativity; STN = subthalamic nucleus; TMS = transcranial magnetic stimulation; VP = vascular parkinsonism.

1. Introduction

Parkinson's disease (PD) is a chronic neurodegenerative disease marked by degeneration of the substantia nigra pars compacta (SNpc) and accumulation of aggregated α-synuclein in specific brain stem, spinal cord and cortical regions and characterized by disturbed motor functioning, clinically manifested as bradykinesia, rigidity and resting tremor (Lees et al. , 2009). In addition to the lack of dopamine, which is the major pathophysiological hallmark of the disease, other neurotransmitter systems, such as those involving acetylcholine, noradrenaline and serotonin play a crucial role in the pathophysiology of the disease (Barone, 2010). Many different approaches to study the motor impairment in PD have been applied, one of which is the recording of event-related potentials (ERPs). ERPs are averaged amplitude fluctuations of the ongoing electroencephalographic (EEG) activity that are time locked to certain sensory, motor or cognitive events (Luck, 2014). The procedure is non-invasive and has been employed to study different cognitive and motor phenomena (Picton et al. , 2000) with an excellent temporal resolution. The ERPs can be evoked by external stimuli, or can be 'emitted' by the brain as it processes information to produce a response. Movement-related potentials (MRPs) are ERPs associated with processes of voluntary movement preparation, initiation and execution in different paradigms, with the movement execution encompassing the time immediately after movement completion (Colebatch, 2007). In general, two main types of anticipatory slow waves preceding movements can be distinguished: the Bereitschaftspotential (BP), and the Contingent Negative Variation (CNV). In addition, movement preparation can also be studied by analyzing the lateralized readiness potential (LRP), which is derived by subtracting the ipsilateral from the

contralateral movement-related slow wave activity over the motor cortex. The Stimulus Preceding Negativity (SPN), which is sometimes regarded too as an MRP (Brunia et al. , 2012), was primarily conceptualized by the observation, that a slow negativity similar to the CNV can be seen even without a motor response (Brunia, Boxtel, 2012). SPN will not be discussed here, as this potential is strictly speaking not an MRP; while in MRPs amplitude rises until the time-point of responding, the negative slope in SPN ends before stimulus onset – long before the response onset.

The aim of this review is 1) to give an overview of MRPs in PD by highlighting the major findings from the studies published to date and 2) to highlight possible directions for future research. In each section (e.g. BP, CNV, LRP), the ERP will be first defined, followed by a review of the literature on the corresponding potential in PD. Studies measuring the classical amplitude/latency based approach were included in this review. The cognitive ERPs in PD are reviewed in a separate paper (Seer et al., under review).

2. The Bereitschaftspotential in Parkinson's disease

When a simple voluntary movement (e.g. finger movement) is made, a slowly rising, negative potential appearing 2 to 1 s prior to the movement can be registered in the EEG at central electrodes (Jahanshahi and Hallett, 2002, Shibasaki and Hallett, 2006). This potential – the Bereitschaftspotential – was first described about 50 years ago (Deecke et al. , 1969, Gilden et al. , 1966, Kornhuber and Deecke, 1964, Kornhuber and Deecke, 1965), and it has been broadly accepted in the research and clinical community as a useful tool for exploring motor physiology in neurological populations (Table 1).

A few distinct components can be discerned during the course of the BP (Fig. 1). The first part of BP, starting 2 to 1 s before a movement, is the so-called 'early BP', and has a more diffuse, yet midline distribution over the cortex. The early BP is thought to reflect more general preparation for the forthcoming movement (Jahanshahi and Hallett, 2002, Shibasaki and Hallett, 2006) and its generation has been linked to the pre-supplementary motor area (pre-SMA), supplementary motor area (SMA) and the lateral premotor cortex bilaterally corresponding to the Brodmann area 6 (Brunia, Boxtel, 2012, Shibasaki and Hallett, 2006). The early BP is followed by the 'late BP' (Shibasaki and Hallett, 2006), starting 400-500 ms before the movement, characterized by a sudden shift of the gradient of the negativity at the central electrodes contralateral to side of movement (e.g. C1 and C3 for the right sided movements and C2 and C4 for the left-sided movements according to 10-20 system). This late BP has been related to activation of the primary motor cortex (Brunia, Boxtel, 2012). As we will see later on, there is indeed evidence that these two BP components are functionally related to different brain areas. It is worth noting that in the literature different terminology has been used to refer to these earlier and later phases of the BP (Jahanshahi and Hallett, 2002). Therefore, while 'early BP' has been variably referred to as simply 'BP', 'BP1'(Deecke, Scheid, 1969), or negative slope 1 (NS1), 'late BP' has been referred to as BP2 (Deecke, Scheid, 1969), negative slope (NS') (Shibasaki and Hallett, 2006), negative slope 2 (NS2). The components following late BP – the premotor positivity (PMP) seen 50 ms before the movement, and the motor potential (MP) occurring 10 ms before the movement onset, as well as the post-motor potentials (Shibasaki and Hallett, 2006) – will not be discussed in this review because they have been less investigated in PD.

The major clinical presentation of PD is impairment of movement related to the dysfunction of the basal-ganglia-thalamo-cortical circuits (including the SMA, which is strongly implicated in the generation of the BP) (Jahanshahi and Hallett, 2002). Therefore, it seems reasonable to expect BP alterations in patients with PD. The studies, which have recorded the BP in PD, are summarized in Table 1. Indeed, most of the studies (Dick et al. , 1987, Dick et al. , 1989, Jahanshahi et al. , 1995) reviewed in detail elsewhere (Praamstra et al. , 2002) have found BP amplitude reduction in patients with PD (but see Barrett et al. 1986). In contrast, prolongation of the latency of the BP, regarded as a marker of the slowness of movements in PD, was only infrequently reported (Shibasaki et al. , 1978). As prolonged BP latency in PD was not replicated in later studies, this finding could be a result of the suboptimal averaging methodology used in this early study on BP (Praamstra, Jahanshahi, 2002).

MRP studies have looked in more detail at different aspects of the BP in PD. For example, Dick, Rothwell (1989) found lower amplitude of the early BP and higher amplitude of the late BP in PD patients off dopaminergic medication, interpreted as indicating reduced SMA activity and compensatory activity of M1. In an earlier study from the same group (Dick, Cantello, 1987) by comparing PD patients on and off dopaminergic medication and healthy participants after taking levodopa or a dopaminergic antagonist, the authors found that levodopa administration increased the amplitude of the early BP in both PD patients and healthy controls. In healthy controls, dopaminergic antagonist decreased the amplitude of the early, but not the late BP. In addition, there was no effect of levodopa on the late BP in healthy controls and there was no difference in the peak BP (late BP) between PD off medication and healthy subjects. In contrast, chronic

administration of levodopa in *de novo* PD patients increased the amplitude of the late, but not the early BP (Feve et al. , 1992) (Fig. 2).

Even though the results of the studies presented above differ considerably, the difference in the results could be due to methodological differences, such as acute (Dick, Cantello, 1987) vs. chronic levodopa administration (Feve, Bathien, 1992). Notwithstanding these inconsistencies, both studies suggested that the early BP amplitude reduction in PD is sensitive to dopaminergic medication. Later studies shed light on the different generators of the early vs. late BP components. In a combined PET-EEG study, Jahanshahi, Jenkins (1995) (Fig. 3) compared self-initiated and externally triggered (by auditory cue, see also Kopp et al. (2000)) finger extension movements in PD patients and age-matched healthy participants. In order to control for the effect of the auditory cue, they also presented the same tone 100 ms *after* the self-initiated movements. Strictly speaking, only self-paced voluntary movements are preceded by the BP, as these are not executed in an automatic fashion but with a willful realization of the intention to move at a particular time (Lang, 2002). Any interference with the self-pacing, such as external cueing, interrupts this condition, even though externally-paced movements also produce movement-related cortical negativity prior to movements, which is more precisely designated as a MRP, rather than a BP (Jahanshahi and Hallett, 2002). The results showed that the early and peak BP amplitude was lower in PD than in healthy controls for self-initiated movements, but there was no difference in MRPs for externally triggered movements between the two groups. The electrophysiological findings for the self-initiated movements (lower early BP in PD patients) were accompanied by significantly reduced activation of the SMA in PD relative to healthy controls, which supports the notion that the SMA contributes to the early BP. Further evidence for the dissociation of BP

subcomponents was provided in a study by Cunnington et al. (1995), who tested the effect of external cues on MRPs. By comparing the response on external vs. no cue trials in PD and healthy participants, they found a greatly reduced early MRP in PD. Furthermore, when the cue was present the early MRP was reduced in both PD and healthy participants. These findings were interpreted as suggestive of impaired internal control mechanisms in PD dependent on the SMA. Namely, the coordination of an internally guided movement sequence comes from the basal ganglia that project to the SMA, considered as the likely generator of the early MRP (BP) slope. This signal then initiates submovements at appropriate times. This mechanism is therefore insufficient in PD (reduced early MRP compared to healthy controls in non-cued condition), which also makes PD patients more reliant on external cueing in which the coordinating signal bypasses the basal ganglia and the SMA and probably operates by engagement of other parts of the motor cortex, presumably the lateral premotor area (Cunnington, Iansek, 1995). Taken together, the evidence from the studies presented above suggests that the deficit in motor preparation in PD is reflected in the lower BP amplitude, mainly restricted to the early part of the potential. Second, data from PD studies do suggest that there is a functional segregation of different BP subcomponents (e.g. functional dependence of the early BP on the SMA). Third, there is a dopaminergic dependence of BP amplitude, such that administration of dopaminergic medication increases the early BP amplitude.

A study by Filipović et al. (1997) aimed at elucidating the functional significance of the attenuation of the BP amplitude in PD by correlating individual BP amplitudes to different response time measures. They found a negative correlation between the amplitude of the early BP and a specific response latency measure: the difference in response latency between complex and simple reaction time tasks, which

they interpreted as evidence for reduced movement pre-programming in PD patients. However, one of the limitations of research on response selection and motor preparation using RT tasks is the lack of temporal resolution to identify the exact time course of processes that occur between stimulus presentation and response initiation. In another study (Filipović et al. , 2001) they compared the BP in depressed and non-depressed patients with PD. The results showed that both depressed and non-depressed PD patients had lower overall BP amplitudes compared to healthy participants, but there was no evidence of modulation of the BP amplitude as a function of depression in PD. In a more recent study, the effect of neurofeedback (NFB) training for slow cortical potentials on increasing the amplitude of BP was tested in PD and healthy participants (Fumuro et al. , 2013). As expected, PD patients showed lower early BP. In good NFB performers, NFB increased the amplitude of the early BP in both PD and healthy participants, suggesting the potential of NFB training to enhance the excitability of cortical areas related to voluntary movement preparation. Hence, the authors concluded that by helping patients to modulate the BP amplitude, NFB might be a promising means for improving motor performance in PD.

All of the studies mentioned above assessed the BP response during performance of voluntary movements of the upper limb. Vidailhet et al. (1993) recorded the BP response while stepping in a standing position and when moving the feet in a sitting position in PD patients off medication and healthy participants. They found that the BP amplitude preceding stepping movements in a standing position was higher than the BP amplitude preceding feet movements while sitting in healthy participants, but not in PD. This was interpreted as reflecting an impairment of preparation and assembly of the complex sequences of movements necessary to

initiate walking in PD. In a later study by using the same protocol, they found that in patients with isolated gait ignition failure, a condition similar to the freezing of gait phenomenon in PD (Taskapilioglu et al. , 2009), there was an increase of BP amplitude on stepping while standing compared to foot movements while sitting, indicating different mechanisms of isolated gait ignition failure compared to gait ignition failure in PD (Vidailhet et al. , 1995).

The impact of subcortical surgery on the BP has been addressed in a few studies. Limousin et al. (1999) examined the effect of unilateral pallidotomy in PD patients off medication before and three months after surgery. The results showed that there was an increase in the slope of the late BP contralateral to the side of pallidotomy, suggesting that pallidotomy improved mainly the later stages of movement preparation in the limb contralateral to the lesion in the internal segment of the globus pallidus (GPi). In another study comparing six PD patients operated with GPi deep brain stimulation (DBS) to six PD patients operated with subthalamic nucleus (STN) DBS, Brown et al. (1999) failed to find a difference in the amplitude of either the early or late BP between DBS on versus off conditions. A co-occurrence of the pre-movement potentials recorded from the DBS electrodes chronically implanted in the STN and electrodes over the scalp was shown in PD patients while they performed self-paced movements (Paradiso et al. , 2003). The onset latency of MRPs recorded from the STN and from the scalp surface did not differ significantly, indicating a direct involvement of the STN in generation of MRPs.

In summary, there is clear evidence that the BP is affected in PD, mostly reflected in the lower early BP amplitude that can be increased by dopaminergic medication, which in turn suggests a clear dependence of the early BP on the dopaminergic system. This potential has mostly been explored in tasks involving

upper limb movements, but can also precede movements of other body parts, such as lower limbs or tongue movements (Shibasaki and Hallett, 2006). BPs prior to such movements of other body parts have to be explored in more detail in future studies. Similarly, the possibility offered by DBS to experimentally manipulate the functional activity of the basal ganglia-thalamo-cortical circuits should be addressed more extensively in future studies.

3. Contingent Negative Variation in PD

The CNV is a slow negative brain potential that develops between two consecutive stimuli, S1 and S2, where S1 is a warning (contingent, anticipatory) stimulus anticipating the imperative S2 stimulus that signals initiation and execution of a motor response. The CNV represents the neural activity necessary for sensorimotor integration or association and is related to planning or execution of externally-paced, voluntary movements (Brunia, Boxtel, 2012). Data indicate that premotor and prefrontal cortices, including the SMA, as well as the basal ganglia are important in generation of this cortical activity. The early CNV component is more frontally distributed and involves the prefrontal cortex, SMA and cingulate cortex and is linked to the arousal and attention associated with S1. The late CNV has a more central distribution and CNV-like activity can also be recorded from the putamen, implying a crucial importance of the basal ganglia-thalamo-cortical circuits in CNV generation as well (Brunia, Boxtel, 2012). Pharmacologically, the most explicit model for the CNV states that its amplitude is determined by the activity of cholinergic neurons, which are in turn under the control of other neurotransmitters – dopamine, noradrenaline and gamma-aminobutyric acid (Brunia, Boxtel, 2012).

A number of investigators have recorded the CNV in PD (see Table 2). Ikeda et al. (1997) investigated the CNV and BP in patients with PD and Progressive Supranuclear Palsy (PSP) and related MRP amplitudes to the severity of symptoms. The BP and CNV amplitudes for patients with mild symptoms did not differ considerably from those of healthy age-matched controls. However, in patients with severe symptoms, while the BP was normal, the late CNV was very small or absent and it was smaller than in healthy participants. It was concluded that the late CNV rather than the BP reflects the severity of parkinsonian symptoms, and that the dissociation between the two surface negative slow potentials strongly supports the different generating mechanisms at the level of subcortical structures; the late CNV being more related to the basal ganglia, whereas the BP might be more associated with other structures including the cerebellum. Oishi et al. (1995) also compared the CNV and BP in 10 PD and 10 vascular parkinsonism (VP) patients. The early CNV and BP amplitudes were lower in PD and VP patients when compared to healthy controls. Also the latencies of the early and late BP were longer in PD and VP, suggesting impaired voluntary movement programming in both PD and VP patients. In a recent study by measuring the CNV as an electrocortical correlate of preparation for action, Renfroe et al. (2016) tested whether PD patients would be less prepared for action under threat of loss compared to age-matched healthy controls. PD patients showed generally reduced action preparation (i.e. reduced CNV amplitude) compared to healthy participants, but there was no difference between the two groups when additional negative incentives (threat of loss) were added, indicating that even though action preparation is impaired in PD, this is not emotion- or valence specific and that movement preparation in PD may potentially be helped by adding positive incentives.

Similar results were obtained in a study by Wascher et al. (1997), in which they found a lower CNV amplitude and force in PD, but no difference in the lateralized readiness potential (LRP, the latter potential is elaborated in more detail below), reflecting reduced activation of movement preparation, but unimpaired response selection, respectively. In an earlier study Wright et al. (1993) compared 20 PD and 30 age-matched healthy individuals on a simple response time task in which a central arrow cue directed the participants' attention to the probable location of a lateralized target stimulus which was validly or not validly cued. In addition to isolating other non-motor ERP components that are beyond the scope of this review, the most striking finding was diminished CNV amplitudes in PD patients compared to healthy participants, indicating impaired response preparation in PD.

Bötzel et al. (1995) compared PD patients with older and younger healthy controls during execution of simple (SRT) and choice (CRT) reaction time tasks. They found a clear CNV in young healthy individuals, small CNV amplitude in older healthy people and absent CNV in PD patients. In addition, there was also a positive slowly increasing wave frontally whose steepness decreased as a function of task complexity and age in controls, but not in PD. In PD, the relationship between task complexity and the steepness of the potential was absent or even reversed, with a slightly larger frontal positivity in CRT than in SRT. In addition, in PD the reaction times were disproportionally longer in SRT compared to CRT. The results of this study were interpreted as indicating greater impairment in storing or initiating simple preprogrammed motor responses in the SRT task in PD patients compared to selecting and initiating the motor response in the more complex CRT task. Cunnington et al. (2001) found generally reduced CNV amplitude, a frontal shift of CNV and a particularly pronounced CNV amplitude reduction over the midline and ipsilateral to

the side with greater basal ganglia impairment in PD patients compared to age-matched healthy controls. Similarly, CNV amplitude has been shown to be attenuated in PD patients during performance of a Go/NoGo task (Pulvermüller et al. , 1996).

As for the effect of different clinical manipulations, such as dopaminergic medication or surgical treatment of PD on the CNV amplitude, Amabile et al. (1986) tested 47 PD patients off medication (after a pharmacological washout-period of seven days), and then 15 days and 30 days after the re-start of dopaminergic medication. The CNV amplitude increased after the start of the dopaminergic medication. This was replicated in other studies (Lukhanina et al. , 2006). These results are, therefore, similar to the results for BP indicating dependence of the CNV generation on dopaminergic processes.

Furthermore, Gerschlager et al. (1999) found that the CNV amplitude in PD patients treated with STN DBS was higher on than off stimulation (Fig. 4). In addition, the amplitude was higher in healthy participants compared to PD off stimulation at the frontal and frontocentral electrodes, but not at the electrode sites located more posteriorly (i.e. centrally and parietally). These between-subject differences were diminished when PD patients were on stimulation, indicating improvement of the impaired cortical functioning in PD mainly in the frontal and premotor areas. Gironell et al. (2002) tested eight PD patients before and after unilateral pallidotomy. They recorded ERPs during self-paced finger movements (BP), a Go/NoGo task (CNV), and found an increase of the late BP contralateral to the pallidotomy but no change in CNV suggesting that neurophysiological changes after pallidotomy are mainly in the last stages of movement preparation and execution. A reduction of the early BP and absence of the CNV indicating difficulties in preparing and maintaining preparation for a forthcoming movement were observed

in a patient with accidental bilateral lesions of the globus pallidus (Kuoppamäki et al. , 2005).

In conclusion, the CNV has provided the opportunity of investigating motor preparation in anticipation of imperative stimuli. Similar to the BP, the available data suggest that the CNV amplitude is reduced in PD. This reduction can be restored by either dopaminergic medication or other treatment options, such as STN DBS. In contrast to the BP, the CNV is inherently externally induced, as the movement triggered by the imperative stimulus (S1) is cued by a contingent stimulus (S2). As such, the CNV offers the possibility to use more complex paradigms and experimental designs and addressing questions such as the interaction of the attentional and preparatory motor processes in movement execution. As this potential is pharmacologically related to the cholinergic system, it also offers the possibility to more directly explore the role acetylcholine plays in generation (planning and execution) of movements in PD.

4. The Lateralized Readiness Potential in PD

The BP and CNV do not give a clear picture of lateralized movement-related activity. A procedure of subtracting the ipsilateral from the contralateral EEG activity provides the opportunity to examine with greater precision the cortical activity related to the preparation of the contralateral limb movement initiation. This yields the so-called LRP (Smulders and Miller, 2012). The onset of the LRP has been shown to be a sensitive marker of response preparation, indexing the time at which response preparation becomes selective with respect to the hand. Indeed, CNV is thought to reflect a rather widespread cortical activation not restricted to a specific effector involved in subsequent motor execution and can thus be considered to represent the

non-specific activation aspect of movement preparation. In order to reveal more specific aspects of movement preparation, the activation pattern of the cortex contralateral to the hand initiating and executing the movement has to be examined. This can be achieved by the subtraction procedure [Left hand($Amp_{C4(t)}$-$Amp_{C3(t)}$) + Right Hand($Amp_{C3(t)}$-$Amp_{C4(t)}$)]/2, where Amp_{C3} and Amp_{C4} is the potential at C3 and C4 locations in a specific time interval *t*. The first part of the equation refers to the amplitude of the LRP when a movement of the left hand is required, and the second part of the equation refers to the LRP amplitude when a movement of the right hand is required. As a result, positive values indicate incorrect response tendencies, whereas negative values indicate correct response tendencies. Typically, positive deflections occur relatively early after stimulus onset (particularly in tasks where conflicting response tendencies are induced) and are then followed by negative deflections that occur before the response. When locked to the stimulus, the LRP is considered to be a good measure for the timing (onset latency) and extent (amplitude) of response tendencies and response selection and therefore mainly reflects the 'cognitive' or 'higher order' aspects of movement preparation (Smulders and Miller, 2012).

In PD, the stimulus-locked LRP has been used mainly to explore the processes of action selection in conflictual situations using different tasks, such as the flanker (Falkenstein et al. , 2006, Praamstra et al. , 1998) and Simon tasks (Praamstra and Plat, 2001), (see Table 3). For example, Praamstra et al. (1996) (Fig. 5) compared the CNV and the LRP response in a visual CNV paradigm between PD patients and healthy controls. The CNV amplitude was lower in PD and there was no difference in the temporal LRP parameters (i.e. the onset latency), but the LRP was extended more frontally in PD and was more focal in healthy controls suggesting different cortical organization of movement preparation in PD. They also found evidence of greater

attentional demands elicited by the S1 stimulus in PD, suggestive of greater effort during response preprograming in these patients. The same authors (Praamstra, Stegeman, 1998) compared performance on a flanker task by PD patients and healthy controls. In this paradigm the participants are required to react to a target stimulus (e.g. an arrow pointing to the left) while ignoring task-irrelevant information that is presented simultaneously by flanking stimuli, typically either in a congruent (e.g. flanking arrows pointing to the left) or an incongruent (e.g. flanking arrows pointing to the right) manner. PD patients showed higher amplitude of the initial positive LRP deflection (i.e. incorrect response tendency) on incongruent trials compared to controls. In addition, PD patients also showed longer RTs in incongruent trials than healthy controls. These findings indicated that PD patients are influenced by incongruent information to a larger extent than controls. Furthermore, in general the LRP latency of the negative deflection was shorter for PD than for controls, and this difference was based on shorter LRP latencies in PD patients on congruent trials. These results suggested intricate changes in sensorimotor integration underlying the PD patients' increased dependence on external cues for response initiation that might be related to a possible compensatory mechanism or strategy that evolves with disease progression and incorporates the alterations in cortical physiology caused by the disease. A similar flanker task was used by Falkenstein, Willemssen (2006). In contrast to the findings by Praamstra, Stegeman (1998), Falkenstein, Willemssen (2006) reported lower incorrect response activation (i.e. lower positive LRP deflections) by incongruent flankers in PD patients compared to controls. Further, they found earlier negative LRP onsets on incongruent trials in PD patients compared to controls. These divergent results across studies may be attributed to differences in the tasks used in the two studies and to the fact that Falkenstein, Willemssen (2006)

tested the patients on medication, whereas Praamstra, Stegeman (1998) tested the participants off medication. The flanker task was also used by Rustamov et al. (2013), who showed that patients with PD and healthy controls show similar congruency effects as judged by RTs, and the initial positive deflection of the LRP. However, these measures were modulated by sequential effects of stimulus congruency across consecutive stimuli ('congruency sequence effect', see Rustamov, Rodriguez-Raecke (2013) for detailed explanation) in controls, but not in PD patients. This pattern of results indicates a lack of adaptive modulation over time (cognitive inflexibility) with relatively spared abilities to instantaneously exert control over action selection.

Praamstra and Plat (2001) used the Simon stimulus-response compatibility task, where on some trials, the spatial position of the stimulus is incompatible with the required response, hence producing conflict and prolonging RTs. They showed that inhibitory modulation of the automatic, stimulus-driven, visuomotor activation of the incorrect response occurs after the initial sensory activation of motor cortical areas. In this study RTs were shorter in PD than in healthy controls. Moreover, in contrast to healthy controls, the LRP amplitude but not the LRP latency was higher in both compatible and incompatible trials for PD patients. Therefore, the visuospatial positioning of the target stimuli was accompanied by activity over the motor cortex with similar latencies but enhanced amplitude in PD patients compared to controls.

Longer RTs and delayed LRPs were recorded in PD patients compared to healthy participants in a study employing a choice reaction time task, indicating both motor and premotor slowing in PD (Low et al. , 2002). By using LRPs and the masked priming paradigm (masked subliminal presentation of visual stimuli), Seiss and Praamstra (2004) evaluated covert inhibition in PD and young and elderly healthy controls. They found that while for young controls covert response activation induced

by a subliminal prime was inhibited when a 100 ms delay was introduced between the prime and target (so called 'negative compatibility' effect), this covert inhibition was reduced in PD and to a lesser extent for the elderly controls, suggesting that deficient inhibition may contribute to the greater susceptibility of PD patients to response interference.

Taken together, the LRP studies reviewed here suggest further impairment of motor control processes in PD patients, particularly the late preparation of the contralateral motor cortex controlling the responding hand which could not be revealed by using the BP and CNV alone. Indeed, because of the subtraction procedure, this potential has been widely interpreted as a manifestation of the hand specific response activation (Smulders and Miller, 2012), which at the same time offers the possibility to index the exact time of hand-specific response preparation. Therefore, this potential offers the possibility first, to more precisely 'dissect' the time course of motor preparation, response initiation and execution and second, to relate more reliably the electrophysiological (LRP) findings to the experimental effects on RT, which cannot be achieved with such a precision by the use of the other (BP and CNV) MRPs described here.

5. Conclusions and future directions

The advent of MRPs has definitely triggered decades of high quality research in the field of motor physiology in both healthy participants and patients with movement disorders and particularly individuals with PD.

In general, there is strong and consistent agreement across studies that processes reflected by the different ERP components reviewed here, namely the BP, CNV, and LRP are disturbed in PD. This is most commonly seen as attenuated

amplitudes of these potentials in PD patients when compared to healthy controls (especially true for the early BP and the CNV). Importantly, decreased MRP amplitudes in PD appear to be amenable to clinical manipulations, such as dopaminergic treatment or DBS. These effects are sometimes subcomponent-specific, such as a selective increase of the early BP by dopaminergic medication.

An interesting point is that this 'spectrum' of MRPs reveals different properties of motor preparation in PD. While the BP can be regarded as a rather 'pure' motor potential most commonly recorded by time locking to self-paced voluntary movements, the CNV reflects processes of movement preparation in anticipation of imperative stimuli. The essence of the LRP is reflected in the double subtraction procedure (Smulders and Miller, 2012), rendering the choice of tasks that can be used to record this potential quite broad. As quite complex tasks have already been used to trigger LRPs, the potential role of this component to reveal more subtle processes related to motor control is vast, especially taking into account the most prominent advantage of this MRP compared to the others – the fact that it is hand specific (i.e. lateralized). Related to this, it can be regarded as a sensitive marker of response preparation, indexing the time at which response preparation becomes hand specific (Smulders and Miller, 2012).

Although much has been done to date to reveal the different processes represented by the MRPs (Jahanshahi and Hallett, 2002), there are still many unresolved issues that have to be addressed in future studies, especially regarding the functional significance of the potentials, their neuropharmacology and their likely generators (Verleger, 2002). In this regard, studies in PD and other movement disorders are more than welcome, as the knowledge of the pathophysiology of PD may help address questions such as which brain regions contribute to generation of

MRPs and in which way. Furthermore, even though the question of the modulation of the MRPs by different neurotransmitters has been addressed since the early studies (Dick, Cantello, 1987, Dick, Rothwell, 1989), there is still a need for further studies to first, replicate these early findings, and second, to address the question of the modulation of the MRP by other neurotransmitter systems (e.g. acetylcholinergic, noradrenergic, serotoninergic), as it is improbable that the neural processes underlying EEG activity are modulated by a single neurotransmitter only.

A great potential for further research of MRPs in PD and also in healthy controls lies in combining different methodologies – EEG and imaging (Nguyen et al. , 2014, Plichta et al. , 2013), transcranial magnetic stimulation (TMS) (de Tommaso et al. , 2012, Sato et al. , 2015), or MEG – since every technique has strengths and drawbacks. Furthermore, most of the studies completed to date have used a limited number of electrodes restricted to the central and frontocentral motor regions of the scalp to record MRPs. High-density EEG recordings improve the spatial resolution of the EEG which would allow improved investigation of movement preparation processes. We have not discussed frequency domain approaches (Makeig et al. , 2004) in this paper, however their wider application would be of value to gain insights into the brain oscillations underlying MRPs at cortical and subcortical levels (Kühn et al. , 2004, Oswal et al. , 2013, Oswal et al. , 2012, Williams et al. , 2002).

Albeit a few studies have examined the effect of subcortical surgery (lesional or DBS) on MRPs (Brown, Dowsey, 1999, Devos et al. , 2002, Devos et al. , 2004, Gerschlager, Alesch, 1999, Gironell, Rodriguez-Fornells, 2002, Limousin et al. , 1995, Obeso et al. , 2009), there is in general a paucity of studies in PD patients treated with DBS or pallidotomy or subthalamotomy. The well-established fact that the basal ganglia-thalamo-cortical circuits are involved in the generation of these

potentials (Brunia, Boxtel, 2012) makes this line of research particularly interesting. Specifically, there is a lack of studies co-registering the signal from the deep brain nuclei and from the surface of the scalp in the period when the electrodes implanted in the nuclei are externalized for a few days after the operation. The main advantage of this approach is that it gives a possibility to directly correlate and compare the signals derived from generators in the cortex (cortical MRPs) and in the deep brain nuclei (deep brain movement related activity) (Shen, 2014) and it should be exploited more frequently in future.

Another aspect of the MRP research that has to be explored in more detail in future studies is identifying the 'cognitive' processes that contribute to motor preparation, initiation and execution. This calls for the development and use of more specific paradigms that allow more clear dissociation of the processes involved. Movement execution is followed by post-motor movement related potentials (Shibasaki and Hallett, 2006), which to our knowledge have not been explored so far from the perspective of the neurobiological changes typical of PD. In addition, there are only few studies measuring the BP related to lower limb movements in PD (Vidailhet, Atchison, 1995, Vidailhet, Stocchi, 1993), which is understandable considering the fact that it is much easier to record and also to interpret MRPs related to upper limb movements. Nevertheless, MRPs while performing lower limb movements deserve greater attention and may help unravel the mechanisms of phenomena such as festination or freezing of gait which reflect an interaction between cognitive and motor deficits of PD.

In conclusion, MRPs have considerably improved our knowledge in understanding the physiology and pathophysiology of motor processes in general (Jahanshahi and Hallett, 2002) and also in PD as reviewed here. However, even more

than 50 years after the first description of the BP (Deecke, Scheid, 1969) there are still many outstanding questions that need to be addressed in future studies.

Conflict of Interest Statement

None of the authors have potential conflicts of interest to be disclosed.

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Figure Legends

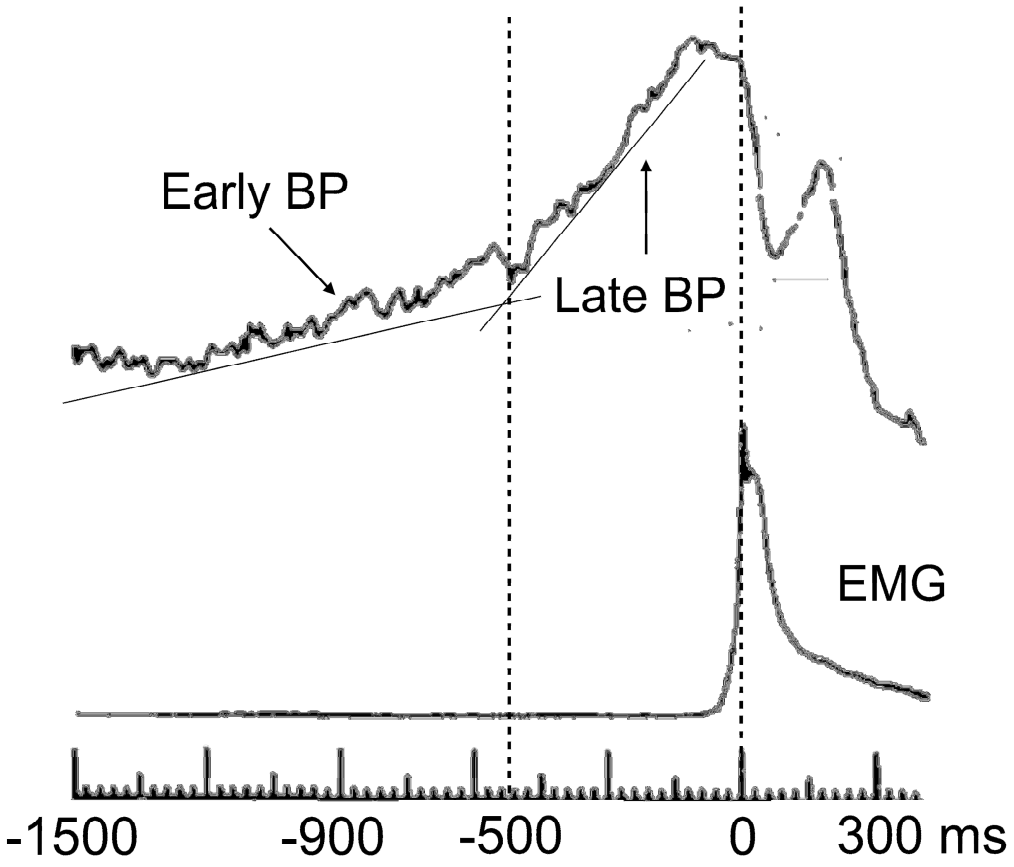
Fig. 1. Bereitschaftspotential (BP) averaged across 14 normal subjects during execution of voluntary, self-paced middle-finger movements. The early BP merges into the late BP at the point of steeper amplitude increase, in this case at around 500 ms. The averaged EMG recording is shown at the bottom part of the figure; the movements starts at 0 ms. The horizontal axis represents time in milliseconds (ms); from Shibasaki et al. (1980), adapted with permission.

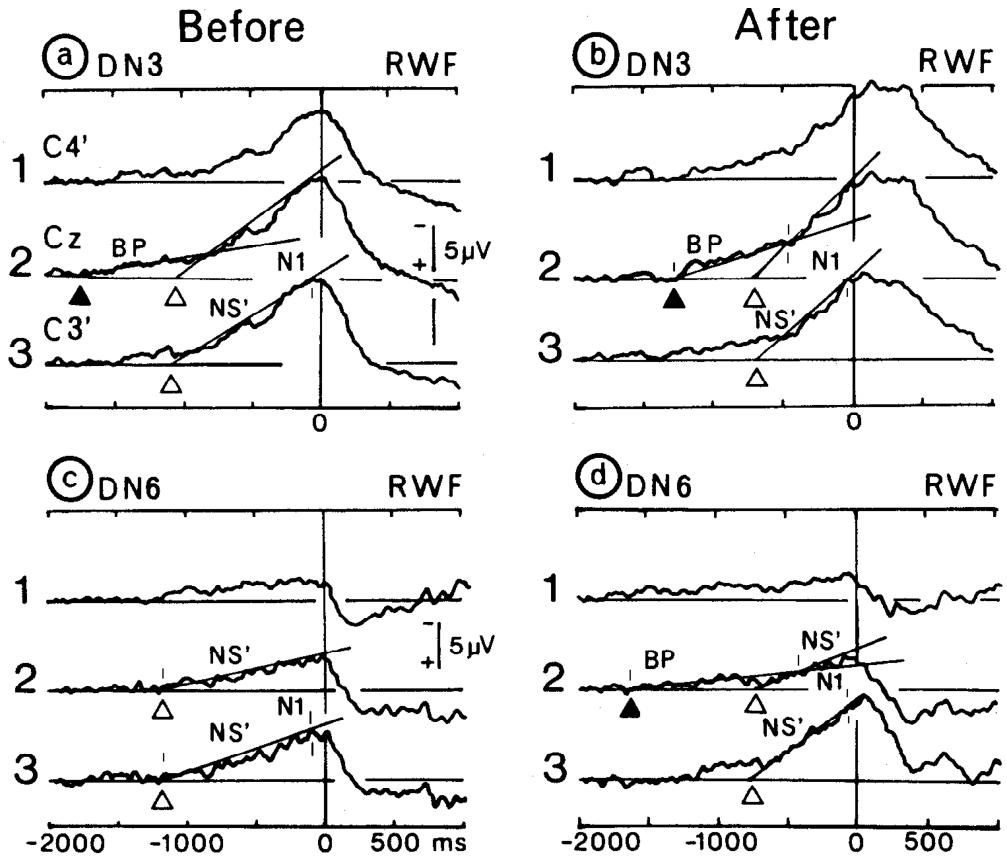
Fig. 2. Bereitschaftspotential (BP) recordings before (a, c) and after three months (b, d) of levodopa treatment in PD in two patients with PD (DN3 and DN6), at one centimeter anterior to C4 (C4'), Cz and one centimeter anterior to C3 (C3'); NS = negative slope, corresponding to the late BP, RWF = right wrist flexion. Black triangles indicate the onset of early BP, white triangles indicate the onset of late BP. Chronic administration of levodopa increases late BP, but not early BP amplitudes; from Feve, Bathien (1992), reproduced with permission.

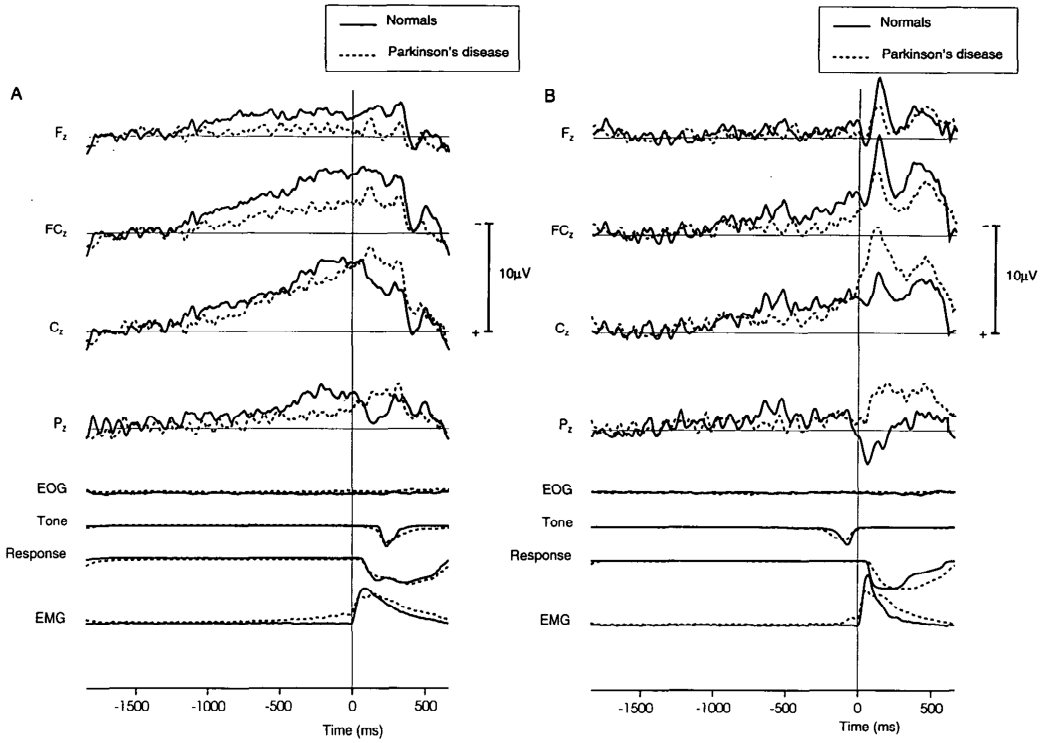
Fig. 3. Grand averages of MRPs preceding self-initiated movements (A) and externally triggered movements (B) for the normal subjects (continuous line) and the patients with Parkinson's disease (broken line). While the amplitude of the late negativities triggered by anticipation of the regular presentation of the stimulus do not differ between PD patients and controls when movements are externally triggered, PD patients show attenuated early and late BP amplitudes preceding self-initiated movements; from Jahanshahi, Jenkins (1995), reproduced with permission.

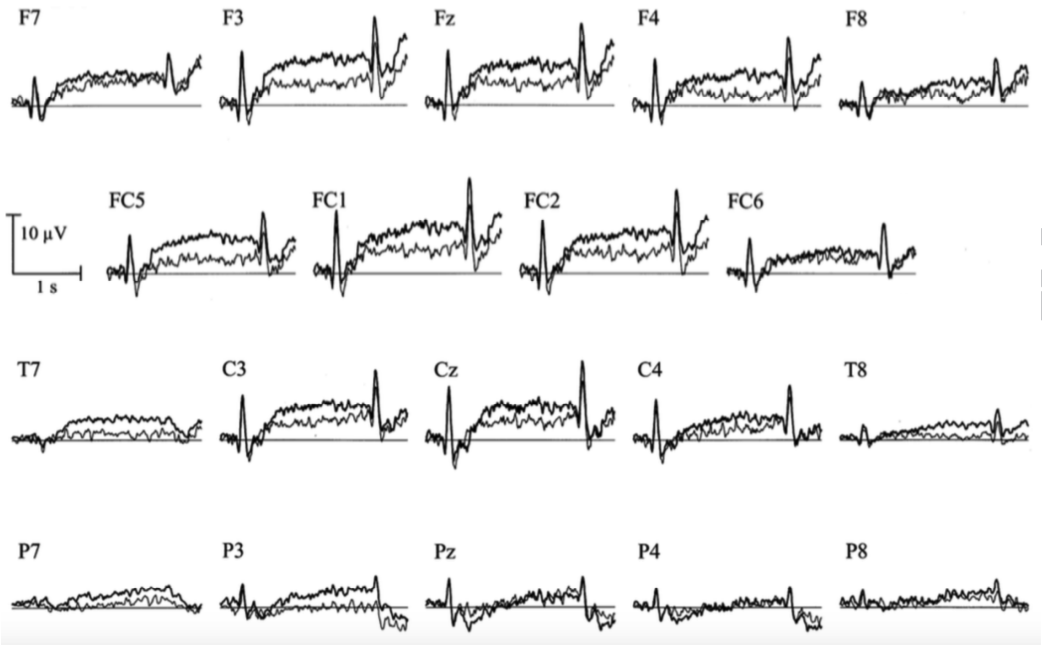
Fig. 4. Mean CNV amplitude for PD patients with STN DBS on (thick line) and STN DBS off (thin line). Potentials are shown from 200 ms before the warning stimulus until 600 ms after the imperative stimulus (total duration of 2.8 s). CNV amplitudes are higher on compared to off STN DBS; from Gerschlager, Alesch (1999), reproduced with permission.

Fig. 5. Lateralized readiness potentials (LRPs) recorded when a cue provided information about the response side (continuous line) and when a cue was non-informative (dashed line). No differences in LRP onset latency was observed between PD patients and controls, from Praamstra, Meyer (1996) reproduced with permission.









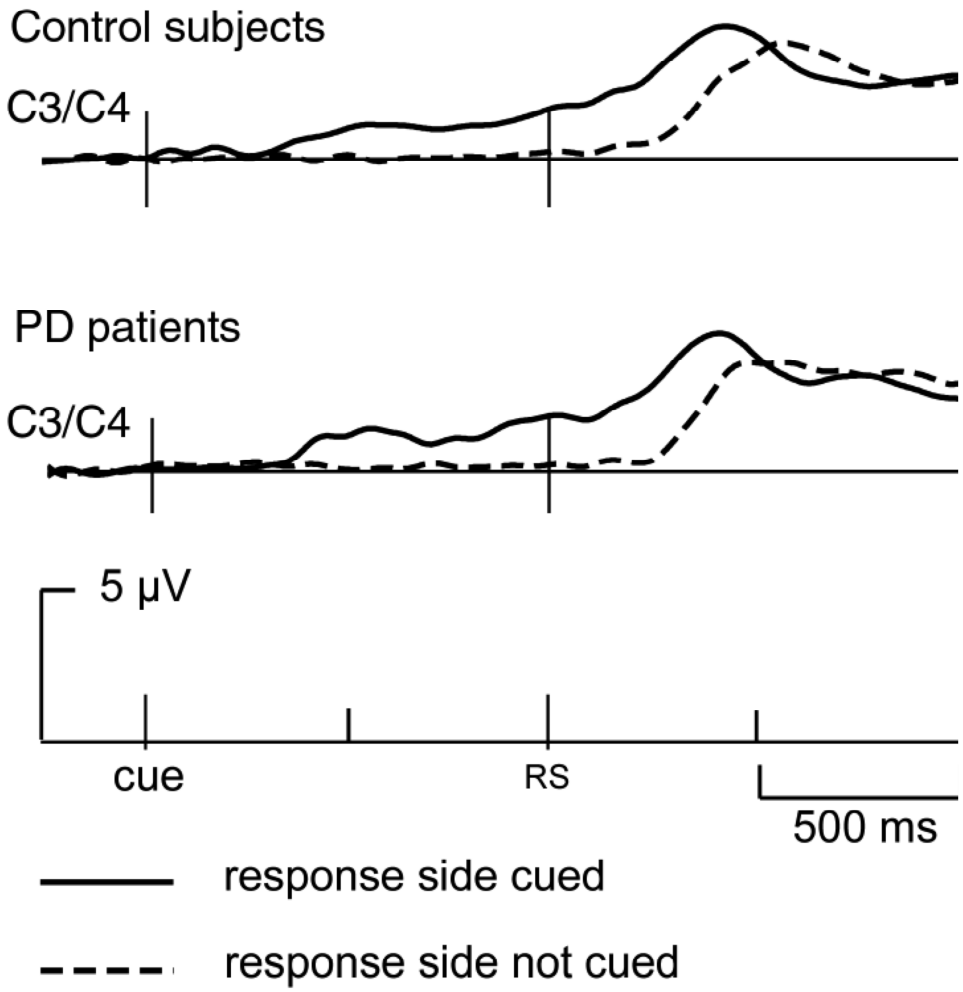


Table 1. Studies on the Bereitschaftspotential reviewed in the paper. Only studies discussed in detail in the paper are listed here; other studies are cited in text.

Bereitschaftspotential			
Reference	**Number of participants**	**Other methodological issues**	**Main findings**
Brown et al. (1999)	6 PD GPi DBS and 6 PD STN DBS	Patients tested OFF DM, SRT, CRT, pegboard, tapping task, flex task	No difference in early or late BP after GPi or STN DBS
Barrett et al. (1986)	10 PD patients compared to HC from previous studies	Patients tested OFF DM	No differences in MRPs between PD and HC
Cunnington et al. (1995)	21 PD patients, 21 HC	Patients tested OFF DM, External cues vs. no cues conditions	Reduced early MRP in PD compared to HC, reduced early MRP reduction in both PD and HC
Dick et al. (1987)	14 PD patients, 13 HC	PD patients tested ON and OFF DM; HC tested on L-dopa and dopamine antagonists; Self-paced upper limb movements	L-dopa induces increase of the early BP in PD and HC, dopamine antagonists induce decrease of early BP in HC; no effect of L-dopa and antagonist on late BP, no difference in the peak BP (and late BP) between PD OFF DM and HC
Dick et al. (1989)	14 PD patients, 12 HC	Patients tested OFF DM; Self-paced upper limb movements	Lower early and higher late BP in PD OFF DM
Feve et al. (1992)	8 de novo, and 8 already treated PD patients	Both group of patients tested ON and OFF DM; Self-paced upper limb movements	After 3 months of L-dopa treatment, late BP increased in de novo PD; in already treated PD on L-dopa late BP was higher than off L-dopa
Filipović et al. (1997)	15 PD patients	Drug naïve patients, SRT, CRT	A negative correlation between the amplitude of the early BP the difference in response latency between (CRT-SRT), suggesting reduced movement pre-programming in PD
Filipović et al. (2001)	16 (8 depressed, 8 non-depressed) PD patients, 8 HC	Patients tested OFF DM	Smaller BP in PD patients than HC, no difference between depressed and non-depressed patients
Fumuro et al. (2013)	10 PD patients, 22 HC	Patients tested OFF DM; NFB for slow	PD patients lower early BP than HC, NFB

		EEG potentials	increased the early BP in both PD and HC in good NFB performers
Jahanshahi et al. (1995)	6 PD patients, 6 HC	Patients tested ON DM; Self initiated vs. externally guided upper limb movements; EEG-PET study	Early and peak BP lower in PD patients than HC in self-initiated movements, no difference in MRPs between groups for externally triggered movements; for PD and HC lower early and peak BP for externally triggered movements; lower activation of SMA (PET) in PD associated with in lower BP compared in PD
Limousin et al. (1999)	27 pallidotomy PD patients	Patients tested OFF DM, before and 3 months after surgery, self initiated hand movements, + SRT/CRT, pegboard and finger tapping	Increase of late BP contralateral to pallidotomy-> pallidotomy improves mainly the later stages of movement preparation and the execution of proximal movements with the contralesional limb
Paradiso et al. (2002)	13 STN DSB PD patients	Patients tested ON DM; Self-paced brisk movements, patients tested on-DBS only	MRP activity with an onset not significantly different than the scalp recorded MRP -> the STN or nearby structures are active before self-paced movements?
Vidailhet et al. (1993)	10 PD patients, 10 HC	Patients ON DM, Standing-stepping and sitting-foot movements while sitting	BP preceding standing-stepping movements higher than sitting-foot movement in HC, but not in PD, suggesting impaired preparation and assembly of the complex sequences of movement necessary to initiate walking
Vidailhet et al. (1995)	4 patients with gait ignition failure	Standing stepping and sitting-foot movement	Increase of BP on standing-stepping compared to sitting-foot movements in isolated gait ignition failure, suggesting different mechanisms of isolated gait ignition failure compared to ignition failure in PD

BP = Bereitschaftspotential; CPT = Continuous Performance Task; CRT = Choice Reaction Time Task; DBS=Deep Brain Stimulation; DM=Dopaminergic Medication; HC = Healthy control; GPi=Globus pallidus interna; MRP=Movement Related Potentials; SRT=Simple Reaction Time Task, STN=Subthalamic Nucleus; PET=Positron Emission Tomography; PD = Parkinson's disease; RT = Reaction Time; SRT= Simple Reaction Time Task

Table 2. Studies on the Contingent Negative Variation reviewed in the paper. Only studies discussed in detail in the paper are listed here; more studies are cited in text.

Contingent Negative Variation			
Reference	**Number of participants**	**Other methodological issues**	**Main findings**
Amabile et al. (1986)	47 PD patients	Patients OFF DM, (after a wash-out period of 7 days), and then 15 and 30 days after the re-start of dopaminergic medication	Higher CNV amplitude after reintroduction of dopaminergic medication
Bötzel et al. (1995)	12 PD patients, 12 HC – young and older	Patients OFF DM, SRT and CRT	Clear CNV in young HC, small in older HC and absent in PD
Cunnington et al. (2001)	14 PD patients, 15 HC	Patients OFF DM, Go/NoGo task	Reduced CNV amplitude shifted frontally in PD compared to HC
Gerschlager et al. (1999)	10 PD patients, 10 HC	Patients OFF DM, ON and OFF STN DBS, Go/NoGo CRT	CNV amplitude for STN DBS ON higher than OFF stimulation; in HC higher than in PD OFF stimulation
Gironell et al. (2002)	8 PD patients	Patients OFF DM, Before and after unilateral pallidotomy; self-paced finger movements for BP; Go/NoGo for CNV	Increase of late BP contralateral to pallidotomy, no change in CNV, suggesting neurophysiological changes after pallidotomy mainly in the later stages of movement preparation and execution
Ikeda et al. (1997)	13 patients with parkinsonism (9 PD and 4 PSP), 10 HC	Patients tested ON DM	In patients with mild symptoms BP and CNV were not different than HC; in patients with severe symptoms BP was the same as in HC, late CNV was very small or absent and it was smaller than HC
Kuoppamäki et al. (2005)	A case study, bilateral posterolateral accidental	MRI, RT task, pegboard and finger tapping tasks, flex and squeeze tasks, self	Early BP and CNV were absent prior to movements, suggesting difficulties in preparing

	pallidotomy resulting in secondary parkinsonism	initiated movements for BP and ready-Go task for CNV	and maintaining preparation for a forthcoming movement
Oishi et al. (1995)	10 PD patients, 10 vascular parkinsonism (VP) and 10 HC	Patients tested OFF DM, and after administration of L-dopa i.v.; BP and CNV recorded	Early CNV and BP amplitude lower in PD and VP than HC; latency of early and late BP was longer in PD and VP than HC, L-dopa improved these differences
Pulvermüller et al. (1996)	18 PD patients, 14 HC	Patients tested ON DM, CPT Go/NoGo paradigm	Lower CNV amplitude in PD
Renfroe et al. (2016)	18 PD patients, 15 HC	Patients tested ON DM	Reduced CNV in PD, no difference between PD and HC when emotional incentives were added
Wascher et al. (1997)	15 PD patients, 15 HC	Patients tested OFF DM, Clock cued CRT, CNV and LRP	Lower CNV amplitude and force in PD, no difference in LRP, suggesting reduced activation of movement preparation, but unimpaired response selection
Wright et al. (1993)	20 PD patients, 30 HC	Patients tested ON DM, SRT	PD had diminished CNV amplitudes compared to HC

BP = Bereitschaftspotential; CPT = Continuous Performance Task; CRT = Choice Reaction Time Task; DBS=Deep Brain Stimulation; DM=Dopaminergic Medication; HC = Healthy control; LRP=Lateralized Readiness Potential; MRP=Movement Related Potentials; SRT=Simple Reaction Time Task, STN=Subthalamic Nucleus; PD = Parkinson's disease; RT = Reaction Time; SRT= Simple Reaction Time Task

Table 3. Studies on Lateralized Readiness Potential reviewed in the paper. Only studies discussed in detail in the paper are listed here; but other studies are also cited in text.

Lateralized Readiness Potential			
Reference	**Number of participants**	**Other methodological issues**	**Main findings**
Falkenstein et al. (2006)	15 PD patients, 15 HC	Patients tested ON DM, Eriksen flanker task	Lower incorrect early LRP and earlier negative LRP onsets on incongruent trials in PD patients PD than in HC
Low et al. (2002)	12 PD patients, 12 HC	Patients tested ON DM, CRT	Longer RT and delayed onset of LRP in PD compared to HC, suggesting motor and premotor slowing in PD
Praamstra et al. (1996)	10 PD patients, 10 HC	Patients tested ON DM, visual CNV paradigm	Lower CNV amplitude in PD; No difference in the latency between groups; LRP extended more frontally in PD, more focal in HC, suggesting different cortical organization of movement preparation in PD
Praamstra et al. (1998)	7 PD patients, 7 HC	Patients tested OFF DM, Flanker task	PD patients showed higher amplitude of the initial positive LRP deflection, suggesting incorrect response tendency in PD
Praamstra et al. (2001)	8 PD patients, 8 HC,	Patients tested OFF DM, Spatial S-R compatibility task (Simon's task)	Higher LRP amplitude in compatible and incompatible trials in PD, no difference in latency compared to HC
Rustmanov et al. (2013)	20 PD patients, 20 HC	Patients tested ON DM, Flanker task	Similar initial positive LRP deflection (amplitude and latency)
Seiss et al. (2014)	12 PD, 12 age-matched and 10 young HC	Patients tested ON DM, PD patients on medication, masked subliminal presentation visual stimuli task.	No difference in overall LRP amplitude between groups, higher scaled LRP amplitude in PD compared to HC as a result of the higher

			compatibility effect in PD. Latency was longer in older PD and HC

CRT = Choice Reaction Time Task; DM=Dopamine Medication; HC = Healthy control; LRP=Lateralized Readiness Potential; S-R=Stimulus-Response Task; SRT=Simple Reaction Time Task, PD = Parkinson's disease; RT = Reaction Time.