

## A process-model based approach to prospective memory impairment in Parkinson's disease

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### ABSTRACT

The present review discusses the current state of research on the clinical neuropsychology of prospective memory in Parkinson's disease. To do so the paper is divided in two sections. In the first section, we briefly outline key features of the (partly implicit) rationale underlying the available literature on the clinical neuropsychology of prospective memory. Here, we present a conceptual model that guides our approach to the clinical neuropsychology of prospective memory in general and to the effects of Parkinson's disease on prospective memory in particular. In the second section, we use this model to guide our review of the available literature and suggest some open issues and future directions motivated by previous findings and the proposed conceptual model. The review suggests that certain phases of the prospective memory process (intention formation and initiation) are particularly impaired by Parkinson's disease. In addition, it is argued that prospective memory may be preserved when tasks involve specific features (e.g., focal cues) that reduce the need for strategic monitoring processes. In terms of suggestions for future directions, it is noted that intervention studies are needed which target the specific phases of the prospective memory process that are impaired in Parkinson's disease, such as planning interventions. Moreover, it is proposed that prospective memory deficits in Parkinson's disease should be explored in the context of a general impairment in the ability to form an intention and plan or coordinate an appropriate series of actions.

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### 1. Overview and general introduction

Prospective memory (PM) refers to the ability to implement intended actions in the future (e.g., remembering to take medication at appropriate times; see Kliegel, McDaniel, & Einstein, 2008 for a comprehensive overview). While early years of PM research have focused on the communalities and differences between PM and retrospective memory (i.e., the encoding and externally prompted retrieval of episodic information in traditional long-term memory paradigms; e.g., Einstein & McDaniel, 1990, 1996) or have studied the effects of adult aging on PM functioning (Zeintl, Kliegel, & Hofer, 2007; see also Henry, MacLeod, Phillips, & Crawford, 2004; Kliegel, Jäger, & Phillips, 2008, for metaanalytic overviews), recent years have seen a remarkable explosion of research targeting possible impairments in PM functioning across a great range of different neuropsychological populations (cf. Kliegel, Jäger, Altgassen & Shum, 2008, for a first general overview). The present review will serve two aims. The first is to give a comprehensive overview of the available literature on PM functioning in one of those many populations targeted over the last decade, i.e., Parkinson's disease (PD).

PD is a neurodegenerative disease that afflicts approximately 0.3% of the entire population in industrialised countries and about 1% of people over 60 years of age (de Lau & Breteler, 2006). The primary neuropathological markers of PD are cell death in the substantia nigra and the presence of Lewy bodies (Dickson et al., 2009). The resultant depletion of dopamine causes impaired functioning of the basal ganglia and disruptions to cortico-striatal circuitry (Obeso, Rodríguez-Oroz, & Benitez-Temino, 2008). In fact, even early in the course of PD dopamine depletion occurs not only in the basal ganglia but also in the prefrontal cortex (e.g., Cools, 2006). In addition to the hallmark motor symptoms (e.g., tremor, rigidity, and Parkinsonian gait), a variety of impaired cognitive functions are also associated with PD (Bosboom, Stoffers, & Wolters, 2004; Pillon, Boller, Levy, & Dubois, 2001). Due to fronto-striatal circuitry dysfunction, the greatest cognitive impairments associated with PD tend to be for those tasks which rely on the prefrontal cortex, such as measures of executive functioning (Owen, 2004a,b), working memory (Farina et al., 2000; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Owen et al., 1992, 1995; Postle, Jonides, Smith, Corkin, & Growdon, 1997), and planning (Culbertson, Moberg, Duda, Stern, & Weintraub, 2004; Hanes, Andrewes, Smith, & Pantelis, 1996; Lewis, Dove, Robbins, Barker, & Owen, 2003; Owen et al., 1995). Although it is generally believed that memory may be relatively preserved in PD, certain types of memory may be more impaired

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than others. For example, Drag, Bieliauskas, Kaszniak, Bohnen, and Glisky, (2009) recently showed that individuals with PD have preserved recognition memory for sentences that were heard (item memory), but impaired memory for the person who spoke the sentences (source or context memory; Drag et al., 2009). Regarding PM, as we detail below, a range of different frontally mediated executive processes are required for successful performance, including planning, maintaining multiple goals in working memory, interrupting ongoing activities when the intention is to be performed, shifting attention to performing the intended action, and sequencing the execution of the intended action (McDaniel and Einstein, 2007). Components of all of these functions are known to be impaired in individuals with PD (e.g., Pillon et al., 2001). Therefore, investigating PM performance in PD is an important endeavour.

The second aim of this review is to put the (few) available studies, into a broader, more general perspective of a *conceptual outline for a clinical neuropsychology of PM*. To achieve this goal, we will propose a framework for future research that describes certain factors to consider in order to avoid confounding multiple mechanisms (e.g., if more than one of the variables suggested is manipulated, it becomes more difficult to evaluate which variable has an effect on condition-related PM performance). In addition, from an applied perspective, the framework will also serve as a guideline for exploring novel and theory-based approaches in terms of diagnosis and/or treatment. Finally, we will point to areas of overlap between clinical and experimental neuropsychology of PM and suggest ways of using a population variable (i.e., PD) to inform PM theory.

## 2. Basic remarks on a clinical neuropsychology of prospective memory

The *common rationale* for clinical neuropsychological research in PM rests on the observation that PM represents a pervasive real-world memory task that is associated with most *everyday memory problems* (e.g., Kliegel & Martin, 2003). Moreover, PM failures are particularly problematic for maintaining patients' health, social relations and careers (e.g., Smith, Della Sala, Logie, & Maylor, 2000). Specifically, in an earlier review we have argued that because of the high prevalence of day-to-day demands on PM, individuals with PM deficits may be unable to sustain independent living (Kliegel, Mackinlay, & Jäger, 2008). Resting on this general motivation, there are four key questions that have been asked in clinical neuropsychology of PM in general, and in the literature on effects of PD on PM functioning in particular. The first question that has largely dominated the clinical literature on PM across most populations studied is a direct consequence of everyday relevance and disease burden and refers to the descriptive issue of determining whether and how severely a clinical condition is in fact impaired in its PM efficiency.

*Question #1 (Description): Is there a PM impairment in population X?* As we will delineate in more detail in the next section, this has also been the key motivating force for the first studies on PM in PD and it represents the natural first step in a research programme on any clinical population. In order to *structure the descriptive pattern* of PM performance, three dimensions of classifying PM tasks have been used in the literature.

The most prominent classification distinguishes between time-based PM and event-based PM (Einstein & McDaniel, 1996). *Event-based* tasks refer to paradigms in which the cue for the appropriate execution of the PM action is a specific, externally presented event (e.g., the appearance of a specific colleague or a target word on the computer screen), and *time-based* tasks are tasks in which the intended action has to be executed at a specific point in time (e.g., at noon or every 10 min). Often, the first studies in any clinical population examined the degree of impairment in those two task types (Katai, Maruyama, Hashimoto, & Ikeda, 2003, for the

first study on PD or Altgassen, Schmitz-Hübsch, & Kliegel, 2010; Altgassen, Williams, Bölte, & Kliegel, 2009, for Autism Spectrum Disorder). Mostly, those studies have revealed a differential picture with one task type being impaired and the other being spared. For example, Katai et al. (2003) demonstrated event-based tasks to be impaired in PD patients and time-based tasks to be spared; however, the pattern was reversed in two more recent studies by Costa, Peppe, Caltagirone, and Carlesimo (2008) and Raskin et al. (2011) (see similar results for Autism Spectrum Disorder as revealed by Altgassen et al., 2009, 2010).

A second way of structuring the descriptive impairment – that motivated the second study on PM in PD patients (Kliegel, Phillips, Lemke, & Kopp, 2005) – refers to the distinction between *simple, single intention* tasks [such as remembering to ask the experimenter to return a personal item at the end of a session; Rivermead Behavioural Memory Test (RBMT); Wilson, Cockburn, & Baddeley, 1985] and *complex, multi-intention* tasks that require one to plan and carry out several delayed intentions [such as the Six Elements Test from the Behavioural Assessment of the Dysexecutive Syndrome (BADS); Wilson, Alderman, Burgess, Emslie, & Evans, 1996]. While few studies have directly contrasted these task types in clinical populations (see Kliegel, McDaniel, & Einstein, 2000 for an exception in healthy aging), both task types have been widely used in the investigation of clinical neuropsychology of PM. For PD, for example, Kliegel, Zimprich and Eschen (2005) revealed marked impairments only in specific aspects of multi-intention PM: in the planning and encoding of multiple task intentions (see, e.g., Wandschneider et al., 2010, for similar descriptive patterns in Juvenile Myoclonic Epilepsy or Kliegel, Eschen, & Thöne-Otto, 2004, for Traumatic Brain Injury or Shallice & Burgess, 1991, for frontal lobe patients).

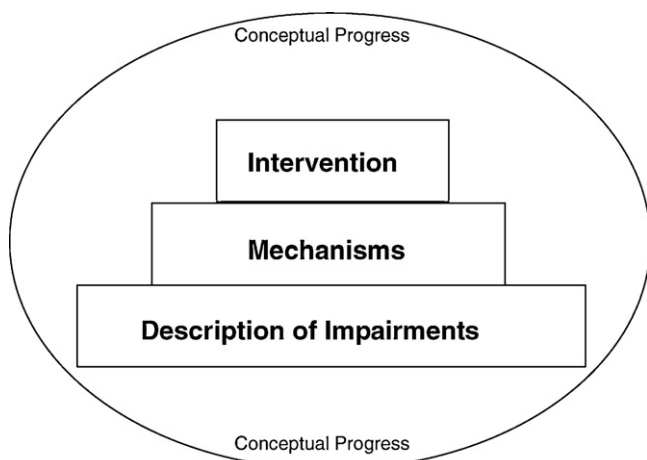
Another multi intention paradigm that has recently received increasing attention in the clinical literature is the Virtual Week task (initially developed by Rendell & Craik, 2000). Besides requiring the execution of multiple intentions in a realistic contextual game setting simulating the course of everyday life, Virtual Week adds another level of descriptive differentiation: extending the traditional time- versus event-based task distinction, Virtual Week separates *regular* from *irregular* PM tasks. Regular tasks represent routine medical tasks (e.g., taking medication at breakfast and 9 p.m.) that are repeated on each day. Irregular tasks represent errand-type tasks that occur while doing normal daily activity (e.g., returning a library book for a friend when you visit the library). The critical features of irregular tasks are that the participants are informed periodically during the game about new PM tasks and the tasks are one-at-a-time tasks that are not repeated. Importantly, similar to time- versus event-based tasks, those task dimensions have often (but not always) resulted in differential patterns of impairment in several clinical populations (see Henry and Rendell, 2009 for a comprehensive review on clinical studies and Rose, Foster, McDaniel, & Rendell, 2010, for application of Virtual Week in PD).

A third descriptive task distinction that has so far only received limited attention in the clinical literature stems from research on adult aging effects. Here, a remarkable pattern has emerged that has been called the *age-PM paradox* (e.g., Rendell & Craik, 2000) and that refers to differential age effects for experimental *laboratory* PM tasks in comparison to *naturalistic* tasks to be performed in participants' *everyday life*. Specifically, research on normal adult aging has revealed age-related *deficits* in standard laboratory-based PM tasks but age-related *benefits* in naturalistic tasks, which are tasks that are carried out in the everyday life of participants (Henry et al., 2004; Phillips, Henry, & Martin, 2008). While no study has so far revealed such a reversed pattern in clinical populations, an increasing number of clinical studies (and recently also on PD; e.g., Foster, McDaniel, Repovs, & Hershey, 2009) have started to

examine PM performance in patients' everyday life and contrast those results with laboratory test performance. This approach is highly important as it tests the prediction that an individual's performance on PM tasks in the lab reflects their ability to perform everyday PM tasks, which simply may not be true (see the age-paradox, Rendell & Craik, 2000). Besides a few studies that actually required patients to perform naturalistic tasks implemented in their everyday routine (e.g., using the Multiple Errand Task; MET; Shallice & Burgess, 1991), most available studies have solely relied on self-report measures of everyday functioning such as the Prospective and Retrospective Memory Questionnaire (PRMQ; Crawford, Smith, Maylor, Della Sala, & Logie, 2003), as in the Foster et al. (2009) study on PD, which are partly limited by response biases and individuals' affect (e.g., Kliegel, Zimprich, et al., 2005; Zeintl, Kliegel, Rast, & Zimprich, 2006).

In sum, the great majority of studies – at least when starting to examine PM in a specific population – has focused on the descriptive question of whether and how severe PM may be impaired in a population such as PD and has used task distinctions to delineate the descriptive pattern as precisely as possible. While we have learned a lot from this approach, one aspect that has been somewhat problematic are the (often) post-hoc conclusions from those patterns. Specifically, differential patterns have mostly been interpreted as indicating more or less controlled attentional resources being involved in the detected impairment (e.g., time-based tasks require more self-initiated monitoring than event-based tasks or irregular tasks requiring more working memory than regular routine tasks). The problem with this approach appears to be that descriptive dimensions are mixed with possible underlying cognitive mechanisms for tasks that may differ in many features (e.g., task difficulty depending on the specific procedure applied). As a consequence, in many clinical populations, this has led to seemingly contradictory findings (see the opposite pattern on time- versus event-based PM in PD revealed by Costa et al., 2008a; Katai et al., 2003; Raskin et al., 2011). Thus, we propose to disentangle both the descriptive and explanatory aspect and suggest adding three further questions to be addressed in the clinical neuropsychology of PM for any population for which at least some descriptive impairment has been revealed (see Fig. 1 for a schematic).

**Question #2 (Mechanisms): Why is there a PM impairment?** The key question that has followed on the descriptive motivation is the issue of which psychological mechanisms underlie the deficits detected: Why are there impairments in PM in populations such as PD patients and where specifically in the process of prospective remembering do they occur? Moreover, why are some aspects of PM possibly spared?



**Fig. 1.** Conceptual progress in clinical neuropsychology of prospective memory.

Several conceptual approaches to theory-driven tests for underlying mechanisms have been suggested. The major approach that our lab has applied to several clinical populations [PD: Kliegel, Phillips, et al., 2005; Kliegel, Zimprich, et al., 2005; TBI: Kliegel et al. (2004); Juvenile Myoclonic Epilepsy: Wandschneider et al. (2010) and also to neuropsychology of adult aging: Kliegel et al. (2000)] focuses on the *multiple phases of the PM process* and the differential involvement of basic cognitive resources such as episodic retrospective memory and executive functioning in those phases. This approach rests on the proposal of a process model which separates the process of prospective remembering into four phases (Kliegel, Martin, McDaniel, & Einstein, 2002; see also Ellis, 1996): (i) *intention formation* – the point at which the intention is formed, which often involves forming a plan, (ii) *intention retention* – a period during which the intention is retained in long-term memory and which is typically filled with an 'ongoing' activity (Ellis & Kvavilashvili, 2000) that precludes continuous rehearsal of the intended task in working memory, (iii) *intention initiation* – the point in time at which execution of the intention is (or ought to be) initiated, and (iv) *intention execution* – where the intended action is executed in accordance with the previously formed plan.

Resting on the motivation of delineating the loci of impairments and determining possible mechanisms of those impairments, we propose using this process model to guide the systematic examination of possible basic cognitive processes and their associated neural correlates underlying the descriptive pattern. The theoretical rationale for expecting differential effects of clinical conditions on the four phases of PM comes from the proposition of specific neuro-cognitive resources being differentially involved in each phase. In proposing an explanatory model (see Fig. 2 for a revised version of a previously presented model that was initially developed for guiding research on lifespan development) we argue that the task features of intention formation, intention initiation, and intention execution components can be assumed to require (specific sets of) executive processes associated with frontally mediated neural networks, whereas the intention retention component may demand mainly retrospective memory storage capacity (associated with hippocampal functioning).

The model postulates that, depending on individual and task characteristics, there are variations in the extent to which a specific mechanism is involved at each phase. Specifically, it is proposed that condition-specific impairments in neuro-cognitive networks that underlie basic cognitive resources such as retrospective memory (mostly mediated by medial temporal networks) and/or executive functioning (mostly mediated by frontal networks) affect each PM phase *through* the task- and individual-specific interplay of several major cognitive variables: planning, storage, monitoring, inhibition and task switching. The general assumption is that condition-related impairments are fully mediated by a *mismatch* between PM task component-specific requirements of cognitive resources (e.g., a PM task may require more or less planning in the intention formation phase) and condition-specific impairments in those resources (e.g., a condition such as PD may lead to more or less available planning resources). Only if the available resources are insufficient for the specific PM task at hand, an impairment is predicted (e.g., even though patients may have reduced planning resources, they may still have sufficient resources for a low planning intensive PM task). While the task-specific requirements depend on the PM phase and other task-related features (as detailed by the multiprocess theory; see below), the resource side depends on the particular neuro-cognitive profile of a given disorder and the specific level of disease progression of a given individual. In the following, we will briefly disentangle those aspects for the four phases proposed.

Planning is assumed to be the most influential variable at the intention formation phase. Importantly for the clinical neuropsychology of PM, specific populations have more or less severe

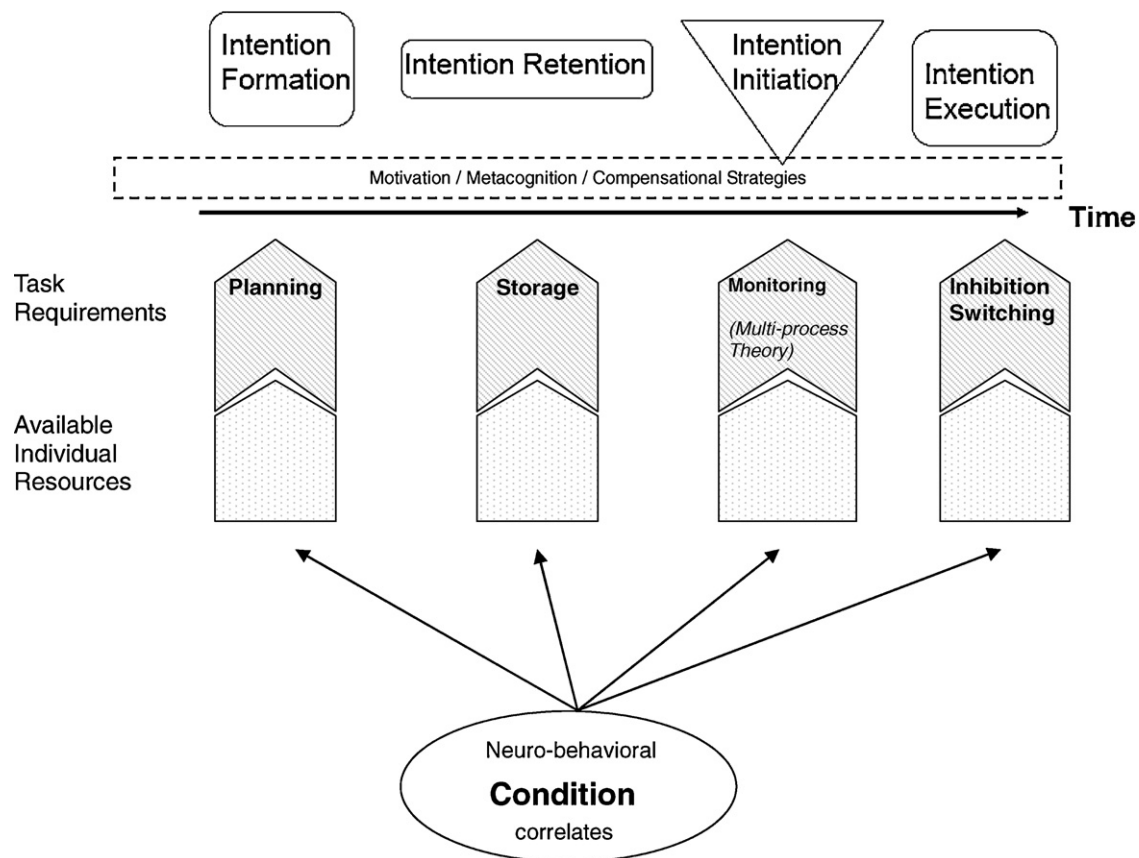


Fig. 2. Process model of prospective memory and associated neuro-cognitive mechanisms.

planning problems that may affect PM performance. For example, in PD, planning deficits represent one of the most consistently revealed impairments (e.g., Dubois & Pillon, 1997; Owen et al., 1992) and have been associated with PD-related dopamine depletion in the striatum and the PFC (e.g., Cools, 2006). In consequence, on the basis of this process-model approach, one would predict particular deficits for PD patients in this phase of PM; and indeed, this is what Kliegel, Phillips, et al. (2005) and Kliegel, Zimprich, et al. (2005) reported in their study on multi-intention PM in PD patients.

Condition-related predictions regarding the *intention retention* component of the model depend on the degree to which a specific condition shows impairment in episodic memory, and on the specific task applied. Most experimental PM tasks place particularly low demands on retrospective memory for the intention content. In the experimental literature this has been suggested to maximize the difference between pro- and retrospective memory. In fact, most experimental tasks were constructed in accordance with Ellis and Kvavilashvili's (2000) suggestion to conduct post-experimental interviews to ensure that only participants who remembered the retrospective component are included in data analysis. Thus, many experimental procedures available were not designed to detect retrospective memory deficits in PM and are likely to underestimate the involvement of retrospective storage capacity on the PM impairment in clinical studies. Using more complex and retrospective memory demanding multi-intention tasks that require the retention of complex plans over a longer delay period, Kliegel, Phillips, et al. (2005) and Kliegel, Zimprich, et al. (2005) demonstrated that PD patients' PM performance was impaired despite their intention retention being largely spared (see also Rose, Foster, Rendell, & McDaniel, 2010b, for similar behavioural findings and see, e.g., Cools, 2006, for a discussion of possible neural correlates for spared stability of mental representations in PD).

The last two phases – *intention initiation* and *execution* – are the two model components on which most traditional laboratory PM paradigms have focused. In terms of executive processes involved, cue detection and subsequent intention retrieval appear to involve monitoring for the target cue (e.g., Smith & Bayen, 2004), inhibition to stop working on the ongoing task (e.g., Bisiacchi, Schiff, Ciccola, & Kliegel, 2009) and cognitive flexibility to switch to the PM task set (e.g., Kliegel, Mackinlay, et al., 2008). However, one very influential model of PM has recently suggested that multiple task features may determine if executive functions are necessary for successful intention initiation and execution. In their "multiprocess framework" of event-based PM, McDaniel and Einstein (2000) have postulated that PM tasks can either be supported by rather automatic or by rather controlled processing. The degree to which controlled attentional processes are required strongly depends on several task-related aspects such as the *focality* of PM cues (e.g., McDaniel, Einstein, & Rendell, 2008). Focal PM tasks are those in which the ongoing task involves processing the defining features of the PM cues (e.g., rating words for concreteness while remembering to press a button whenever a specific word appears; Einstein & McDaniel, 1990). It is assumed that, due to processing overlap between the ongoing and the PM task, focal PM cues are sufficiently processed during the ongoing task to enable rather spontaneous or automatic retrieval of the intended action (e.g., the intention seems to "pop into mind" at the appropriate moment). By contrast, in nonfocal PM tasks, the PM cues are not part of the information being extracted while performing the ongoing activity (e.g., working on the aforementioned ongoing word rating task while remembering to press a button whenever the background of the screen shows a particular pattern; Park, Hertzog, Kidder, Morrell, & Mayhorn, 1997). Here, there is little overlap between the ongoing task and the PM cue which signals the appropriateness

for performing the intended action, and so successful prospective remembering more strongly demands executive attentional and working memory resources to monitor for the PM cue. The straightforward prediction for the clinical neuropsychology of PM is that populations such as PD patients showing marked executive impairments due to dopamine depletion in frontal and cortico-striatal networks (Cools, 2006) will show PM deficits (only or particularly) for tasks with nonfocal cues because the situation places high demands on executive functions. Confirming this conceptual prediction, a recent study on PD patients by Foster et al. (2009) nicely revealed this pattern. Moreover, from a broader perspective, this finding not only confirms the specific prediction of the multiprocess framework for PM retrieval, but also supports the general idea of a mediational mechanism in the process model proposed here; namely that clinical impairments will emerge in (specific phases of) PM only if the interplay between task requirements (high executive load, as in nonfocal tasks) and the condition-related availability of phase-specific cognitive resources (reduced executive control, as in PD) lead to a mismatch.

An alternative, but mostly complementary, perspective on the differentiation of phases and resources involved in PM that has guided some clinical studies (also in PD; e.g. Costa et al., 2008a) is the distinction between a *prospective and a retrospective component* in PM (Guynn, McDaniel, & Einstein, 2001; Simons, Schölvinck, Gilbert, Frith, & Burgess, 2006). In this literature, the prospective component refers to those processes that support the detection or recognition of prospective cues (intention initiation phase), while the retrospective component entails processes that support the retrieval of an intention from long-term memory following the recognition of a prospective cue (intention retention and partly intention execution phase; Einstein & McDaniel, 1996; Smith & Bayen, 2004). Research on those components has shown that the prospective component is more sensitive to individual differences in executive functioning and working memory capacity (Rose, Rendell, McDaniel, Aberle, & Kliegel, 2010; Smith and Bayen, 2005) or variation in the working memory demands of the ongoing activity (Marsh & Hicks, 1998; West, Bowry, & Krompinger, 2006) than the retrospective component. In addition, the retrospective component appears to share many of the processes that support explicit episodic memory in recognition and cued-recall tasks and that facilitate the retrieval of contextual information from long-term memory (Einstein & McDaniel, 1996; Guynn et al., 2001; Smith & Bayen, 2004; West & Krompinger, 2005). The general division between prospective and retrospective processing components is also supported by evidence from studies examining the neural basis of PM. With respect to the retrospective component, it has been shown that patients with damage to the medial temporal lobe can exhibit deficits in both PM tasks and episodic memory tasks (Palmer & McDonald, 2000). Moreover, there is some evidence that indicates that regions of the medial temporal lobe are activated by the realization of delayed intentions (Okuda et al., 1998). These findings are consistent with the idea that there is overlap between the processes underlying the retrospective component of PM and varieties of explicit episodic memory including recognition and cued-recall (Einstein & McDaniel, 1996; West & Krompinger, 2005). In contrast to the retrospective component, processes underlying the prospective component may be more heavily dependent on the functional integrity of the prefrontal cortex. Evidence from neuroimaging (Burgess, Quayle, & Frith, 2001; Burgess, Scott, & Frith, 2003; Simons et al., 2006) and patient studies (Burgess, Veitch, de Lacy Costello, & Shallice, 2000; Cockburn, 1995; Palmer & McDonald, 2000) underline the importance of frontal structures for PM performance. Specifically, an increasing amount of evidence suggests that the prospective detection of PM target cues is dependent on the frontostriato-thalamo-cortical loops (which are disrupted in PD; Cools, 2006). The role of prefrontal

systems in the prospective component has been specified by neuroimaging and ERP studies, which have implicated the fronto-polar and superior rostral aspects of the frontal lobes, particularly Brodmann's area 10 (e.g., Burgess et al., 2001, 2003; Zöllig et al., 2007). Overall, the utility of this approach for the predictions of mechanisms being involved in PM impairments in clinical populations does not go over and above those derived in the context of the process model: Impairments in the prospective component are expected, if the neuro-cognitive profile of a disorder mostly shows executive/frontally mediated impairments and impairments in the retrospective component are to be expected for conditions that largely show episodic memory/temporally mediated impairments.

While the conceptual arguments referred to above summarize the most common rationales for studying mechanisms of clinical impairments in PM, we want to briefly outline possible extensions to our initially suggested model and thereby raise some first issues for future research. So far, the mismatch assumption has been a rather *static* idea suggesting that the amount of available resources may either be sufficient (no impairment) or insufficient (impairment) for particular PM phases and their task-specific resource requirements. Similarly, in studies adopting either the multiprocess theory approach (e.g., comparing focal versus nonfocal PM task) or targeting the prospective and retrospective component of PM, the general assumption was that a clinical population may be impaired due to limited available cognitive resources caused by a specific neuro-cognitive pathology. This rationale mostly neglects that non-cognitive factors such as *motivation* and/or *metacognitive awareness* of one's own limitations and potential may enable individuals to pro-actively change the task requirements. For example, one may redefine more difficult tasks such as time-based tasks into easier event-based tasks – instead of trying to remember to take medication at 8 p.m., one may link the task to an event such as dinner or an alarm clock. While such compensatory mechanisms are largely prevented in typical laboratory tasks, they are likely to occur in everyday life and may enable patients to preserve their everyday functioning longer than one would predict based on their laboratory test performance. Moreover, motivational biases (e.g., being more motivated by important intentions) and metacognitive beliefs (e.g., knowing about one's tendency to forget specific tasks) may lead to patients strategically focussing their available resources on task relevant aspects. This is especially relevant in PM as it is a dual-task situation requiring one to divide attentional resources between the PM and the ongoing task (e.g., Kliegel, Martin, McDaniel, & Einstein, 2001; Kliegel et al., 2004). The clinical relevance of this argument has been initially demonstrated in the context of PD when Altgassen, Zöllig, Kopp, Mackinlay, and Kliegel (2007) showed that patients were in fact perfectly able to perform the very same PM task if the task constraints (via importance manipulations) led patients to focus on the PM task, whereas they were impaired in this task when instructed to focus on the ongoing task. Although no study has addressed this issue in everyday life, it is likely that metacognitive beliefs of one's own abilities and about task priorities will affect individuals' resource allocation policy, which will affect the extent to which a PM impairment is observed. This leads to the final two questions of a clinical neuropsychology of PM.

*Question #3 (Intervention): What can we do about the PM impairment?* The ultimate aim of the clinical perspective on neuropsychology of PM is the development of intervention programs. So far, however, clinical trials are rare in PM, possibly reflecting the diversity and heterogeneity of the descriptive pattern and the paucity of proper studies targeting the mechanisms of PM impairment. In PD patients, so far no intervention study has been published; however, results obtained in the context of the first two questions may help to lay the ground work for future studies in this regard. Decomposing the process of PM has shown that some phases are

more affected than others (intention formation versus retention; see Kliegel, Phillips, et al., 2005; Kliegel, Zimprich, et al., 2005). This suggests that traditional memory training interventions that focus on strategies to improve episodic (retrospective) memory are not likely to be an effective approach for treating PM impairments in PD. Rather, strategies that facilitate the encoding and planning of PM tasks such as implementation intentions (which have been shown to be effective in reducing intention formation deficits in old age; see Kliegel, Martin, McDaniel, Einstein, & Moor, 2007; Liu & Park, 2004) may be more successful given the initial results on the loci of PM impairment in PD. Altgassen et al.'s (2007) data also suggest that the way individuals may make use of their (limited) resources can be an angle to improve PM performance in PD patients. In some situations, simply focussing on the PM task (and thereby downgrading the importance of the ongoing activity) may help to ensure appropriate implementation of the intended action.

In general, resting on the mismatch idea of the process model, two (complementary) starting points seem appropriate. Within the phase detected to be most impaired in PD, an evidence-based intervention may either target the task characteristics (e.g., reduce the need for planning, use regular and/or focal cues) or may directly target the available resources [e.g., either by optimizing resource allocation strategies (Altgassen et al., 2007), or by pharmacological interventions – as suggested by Costa et al. (2008b), based on findings on the positive effects of L-Dopa]. Alternatively, recent attempts to directly train working memory and executive control functions may be a third, complementary approach that holds promise (see Klingberg, 2010, for an overview of first promising results, mostly obtained in healthy individuals).

*Question #4 (Conceptual advancement): What can theoretical models learn from clinical studies?* The final question is not an additional question per se, but aims at encouraging direct exchange between the more applied clinical perspective and basic experimental research which will advance both fields. Although clinical and basic research are mostly conducted in specialized labs, focussing on either perspective, research on the clinical neuropsychology of PM that aims at all three questions has been most successful in informing the conceptual debate on PM in general. All models summarized above have mainly been developed in the context of cognitive or developmental research perspectives. However, as indicated, they clearly allow for model-based predictions such as testing the focality assumption (e.g., Foster et al., 2009) or disentangling the phases of PM (e.g., Kliegel, Phillips, et al., 2005; Kliegel, Zimprich, et al., 2005) in clinical settings. In demonstrating differential effects of clinical conditions based on theory-driven hypotheses, the research community will not only learn more and more precisely whether, how, and why disorders such as PD are affected in PM functioning, but those data will also help to shape theoretical models per se and will help to learn more about the neural basis of the concepts proposed (e.g., retrospective versus prospective component). Finally, they will also ultimately reveal limits of current conceptual frameworks in cases where clinical phenomena will not be sufficiently described or explained by current theories of PM.

In light of the general framework developed above, the following section will now present a detailed review on the empirical findings so far available on PM functioning in PD patients. Here, we will elaborate on the specific results of the single studies that were only briefly described when laying out the general picture (see Fig. 3 for an overview of all studies' main effects structured by PM phases).

### 3. Empirical studies

As described above, PD is associated with the depletion of dopamine in basal ganglia and prefrontal cortex which impedes

fronto-striatal brain circuitry (e.g. Middleton & Strick, 2000) and is assumed to underlie PD individuals' deficits in executive functioning (e.g., planning and working memory; Costa et al., 2003; Owen et al., 1995; Owen, 2004a,b). Given these abnormalities in neuro-cognitive functions and processes underlying PM, several studies have investigated prospective remembering in PD as an everyday life indicator of impaired planning and executive control.

Katai et al. (2003) were the first to investigate PM in PD. They applied event- and time-based PM tasks and compared PD individuals' performance with those of healthy older adults. For the ongoing activity, participants were engaged in word and number selection tasks. PM tasks consisted of remembering to tap the desk when cue words were presented ("cow" and "orange"; event-based) or when 10 and 15 min had passed (time-based). To monitor the elapsing time, participants could check a digital clock that was located behind their back. Besides ongoing task performance, for each PM task separate scores for the retrospective and the prospective component were calculated. Retrospective memory for the PM task was assessed based on participants' ability to recall the task instructions, while the PM scores referred to initiating the PM tasks at the appropriate moments. Importantly, significant group differences only emerged with respect to the event-based PM tasks, with PD patients showing reduced performance as compared to controls. In contrast, PD individuals were as good as controls in time-based PM, time monitoring, retrospective memory for the prospective intentions, and ongoing task performance. The finding that event-based PM was reduced, despite spared retrospective memory for this task, was interpreted as showing that retrieval of the PM instruction might be impaired while memory for its content is intact. This result may be seen as somewhat surprising given that PD is partly associated with deficits in declarative memory, recognition and recall; however, Katai et al. acknowledged that the task might have been too easy to detect differences in the retrospective component of the PM tasks. Additionally, findings on possible retrospective memory deficits in PD are inconsistent and vary according to disease progression (e.g., Boller & Muggia, 1999; Muslimovic, Post, Speelman, & Schmand, 2005; Whittington, Podd, & Stewart-Williams, 2006). Moreover, conclusions regarding time-based PM performance may be somewhat limited, given that only two time based responses were required and an external cue (a clock) was present, which might have led to a ceiling effect, thereby preventing the detection of possible group differences.

Based on the study of Katai et al. (2003), Kliegel, Phillips, et al. (2005) and Kliegel, Zimprich, et al. (2005) investigated event-based PM in PD using a complex multi-intention paradigm to explore possible deficits in the four phases of prospective remembering and their correlates (such as working memory, attention, episodic memory and inhibition) in individuals with PD and healthy controls. Participants were required to work on six different subtasks according to specified rules and within a restricted time (modified Six Element Task; Kliegel et al., 2000). The experimenter first explained the tasks to the participants and then instructed them to develop a plan on how to later perform them (intention formation phase). After a first filled delay, participants were asked to recall their plans (intention retention phase). Following a second filled delay, participants were instructed to start working on the six tasks on their own initiative upon presentation of a previously explained cue (intention initiation phase). Performance in the intention execution phase was evaluated by means of plan fidelity (i.e., how closely participants followed their original plan) and self-initiated switching between the six tasks. In comparison to controls, participants with PD were impaired in intention formation and intention initiation. While the intention initiation effect mirrored the previous Katai et al. study, the deficit in the intention formation phase is consistent with the general planning deficit in PD (Culbertson et al., 2004; Hanes et al., 1996; Lewis et al., 2003;

### Prospective Memory Process

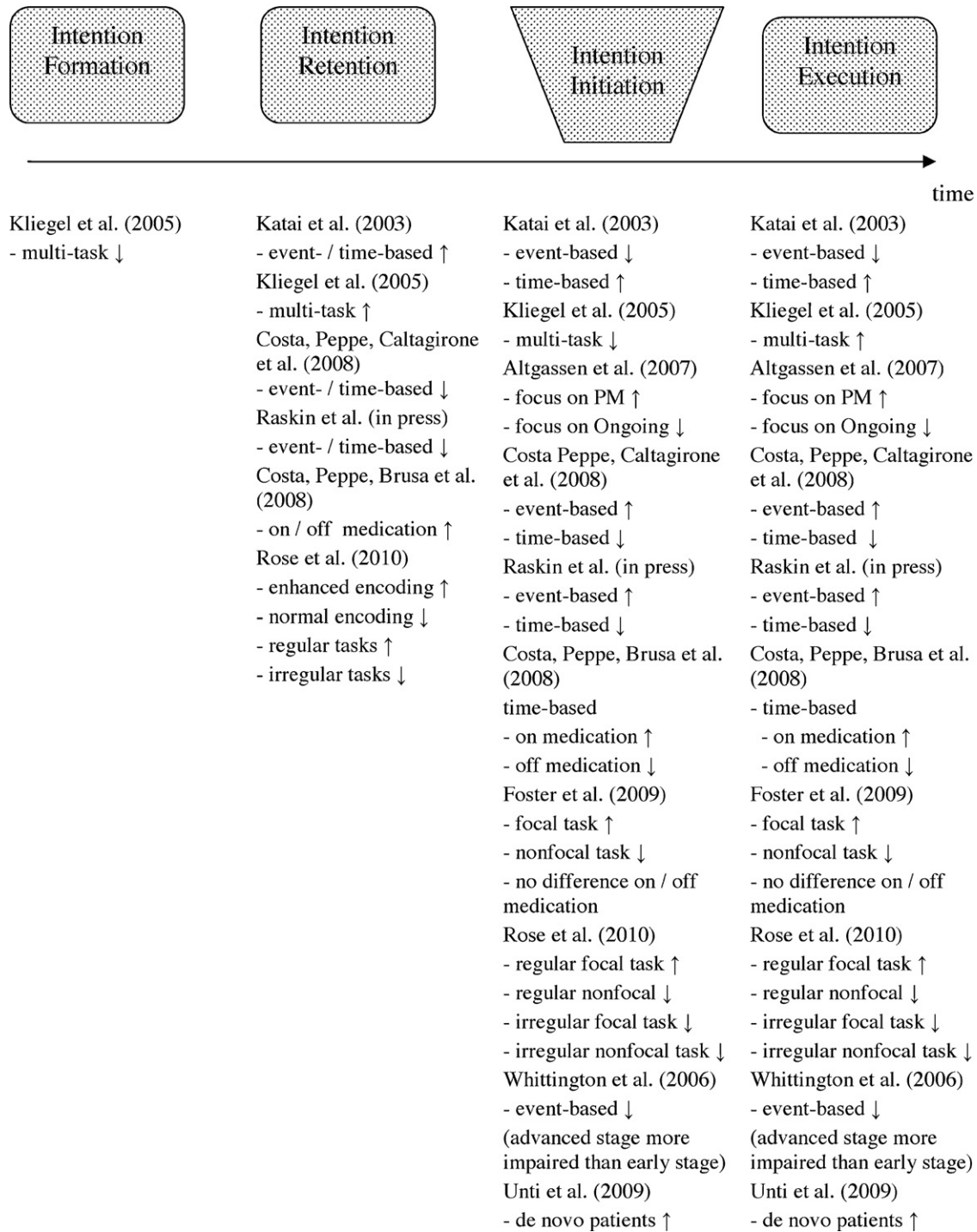


Fig. 3. Empirical evidence on prospective memory in Parkinson's disease organized according to the process model (↓: impaired; ↑: preserved).

Owen et al., 1995) as well as with studies showing a limited use of higher-level encoding strategies, such as semantic clustering during list learning (e.g., Buytenhuijs et al., 1994). By contrast, no group differences emerged with regards to intention retention (as well as plan fidelity) and intention execution (self-initiated switching). Taken together, results were largely in line with Katai and colleagues' study. Both studies observed a deficit in event-based PM and spared retrospective memory for the prospective intention. Importantly, Kliegel et al. demonstrated this directly for the (relatively complex) intention content assessed within the inten-

tion retention delay phase. From a neuro-cognitive perspective on PD, this pattern nicely dovetails with a review by Cools (2006) who has argued that dopamine depletion in PD mainly affects plasticity of representations and thus reduces cognitive flexibility as needed in planning situations but that stability of cognitive representations as needed for intention retention may be relatively spared in early phases of PD. In accordance with this reasoning, working memory capacity was shown to strongly contribute to PM planning performance. While results revealed by Kliegel, Phillips, et al. (2005) and Kliegel, Zimprich, et al. (2005) largely support the process model

proposed in the first section of this review, data were correlational and thus no causal conclusions can be drawn. Thus, studies experimentally varying possible mechanisms are still needed.

Following up on these previous studies, *Altgassen et al. (2007)* was the first study to manipulate a potential cognitive mechanism. They investigated traditional event-based PM, but with a specific focus on the intention formation phase. Considering the planning deficit in PD, the authors hypothesised that PM performance might be improved by externally stressing the importance of the PM task during this phase. This assumption rested on the argument that PM tasks are dual task situations consisting of an ongoing activity and the embedded PM task (see, e.g., *Einstein, Holland, McDaniel, & Guynn, 1992*). Both tasks compete for (limited) attentional resources and empirical evidence has shown that the task that receives more attention is better performed (e.g., *Kliegel et al., 2001*). In the *Altgassen et al.* study, each participant performed two versions of the event-based PM task, one emphasising the importance of the PM task and one emphasising the ongoing task. For the ongoing task, individuals worked on a 2-back letter task, while the PM task consisted of responding to six predefined letters. In addition, working memory and attention were measured as potential underlying factors. As expected, results revealed that individuals with PD were as good as controls in prospective remembering when the importance of the PM task was stressed. In contrast, controls outperformed the PD group when the ongoing activity was stressed. Thus, externally highlighting the importance of the PM task improved PM performance and eliminated the PD impairment. Surprisingly, however, ongoing task performance did not interact with task importance (which is what is usually reported in the experimental literature examining importance effects in PM; *Kliegel et al., 2001, 2004*). Two possible reasons were put forward to explain this discrepancy. Either the task was not sensitive enough to detect a trade-off (e.g., the effects on the ongoing task were too small). Alternatively, the importance effect may not have occurred in the execution phase through redirecting attentional resources from the ongoing task to the PM task when working on both tasks. It may be possible that the importance instruction may have solely altered the encoding in the intention formation phase. According to the intention-superiority literature (e.g., *Goschke & Kuhl, 1993*), intentions are assumed to be encoded in memory with a higher level of activation than other to-be-remembered material. Following this conceptual proposal, the importance effect might be explained by importance instructions leading to especially high activation of the PM cues at the time of encoding (intention formation phase). This might cause enhanced retrieval of the cues in the execution phase through increased activation of the intention without affecting ongoing task performance (supported by the automatic route suggested by the multiprocess framework). In contrast with the latter explanation, however, and consistent with *Kliegel et al.'s (2005)* study, working memory strongly influenced prospective remembering. In fact, covarying working memory reduced the importance effect to non-significance. Taken together, the results of *Altgassen et al.* showed that PM and intention formation may not generally be impaired in patients with PD, but can be preserved with explicit strategic prioritization of intentions during formation.

Given that both, the *Kliegel et al.* and *Altgassen et al.* studies applied rather complex paradigms that put high demands on underlying processes such as retrospective memory, planning and working memory, it is unclear whether the PM deficit in PD was specific to the prospective component or was rather driven by overall task difficulty. To tackle this criticism *Foster et al. (2009)* employed an experimental paradigm that explicitly manipulates whether strategic attentional monitoring was needed for intention retrieval (*Einstein & McDaniel, 2005*) while holding all other task demands equal and reducing ongoing task demands and retro-

spective memory load. Precisely, following up on the multiprocess framework (*McDaniel & Einstein, 2000*), *Foster et al. (2009)* investigated possible impairments in strategic and self-initiated processes especially at retrieval in PD and suggested those effects to be caused by fronto-striatal lesions (*Taylor, Saint-Cyr, & Lang, 1986*). To this end, they varied the demands the PM task put on strategic versus automatic processing by manipulating prospective cues' focality. As indicated earlier, focal cues are assumed to rather automatically trigger retrieval of the planned intention and, importantly, to mainly rely on the medial temporal lobe and surrounding areas – areas which remain somewhat intact in PD, at least in early stages of the disease (however, PD is associated with hippocampal gray matter loss as the disease progresses; *Ibarretxe-Bilbao, Tolosa, Junque, & Marti, 2009*). In contrast, as nonfocal cues require more strategic attentional processes, the neural correlates associated with those PM cues are assumed to be linked to prefrontally mediated networks. Given that the latter are impaired in PD, *Foster et al.* hypothesized that individuals with PD should perform worse on nonfocal event-based PM tasks than on focal tasks.

In addition to this laboratory task, *Foster et al.* explored, for the first time, everyday PM performance in PD with the PRMQ (*Crawford et al., 2003*). Individuals with PD were also tested once while medicated (“on”) and once without antiparkinsonian medication (“off”) and their performance was compared with that of healthy age-matched adults. For the ongoing task, participants performed a word categorisation task. For the focal condition the PM targets were words whereas for the nonfocal condition the PM targets were syllables. As predicted, individuals with PD showed reduced PM performance if task demands on self-initiated processing were high, both in the laboratory (non-focal) and the real world (PRMQ). The latter was reflected in analyses of participants' PRMQ ratings that showed more self-cued memory failures in everyday life in PD. In contrast, no statistically significant differences emerged between groups in the focal condition (however, as possible ceiling effects may have affected the sensitivity to detect the critical interaction, this pattern needs replication). This finding was again supported by the PRMQ, in which patients with PD reported less environment-cued than self-cued failures. There were no significant correlations between individuals' laboratory PM performance and self-ratings in the PRMQ (both with respect to the focal and nonfocal condition), possibly owing to differences in the characteristics of laboratory versus everyday PM tasks or to a restricted range of scores. Additional findings showed that working memory influenced PM performance, especially in the nonfocal condition, which is in line with previous studies (see also *Choudry & Saint-Cyr, 2001*), but medication status did not affect participants' prospective remembering; there were no performance differences „on” and „off” medication.

Further extending the examination of event-based PM and addressing both intention formation and initiation, recently, *Rose, Foster, et al. (2010)* reported findings from a study in which individuals with PD and healthy older adult controls performed the Virtual Week game (*Rose, Rendell, McDaniel, Aberle, & Kliegel, 2010*). Participants were to perform event-based PM tasks that differed in regularity and focality of cues. Tasks were either regular in that they were to be repeatedly performed at the same events (e.g., take medication at breakfast or 9 p.m.) or irregular in that they were to be performed just once, in relation to a specific event (e.g., returning a library book for a friend when you visit the library or phoning a plumber at 4 p.m.). Tasks that were to be performed on “event cards” (e.g., the breakfast event or visit the library event) were considered to have more focal cues than tasks that were to be performed when one's token crossed a particular time square because reading and simulating the activities described on the event cards was central to the ongoing activity of the game, whereas attending to the time square that one's token was on was a more peripheral



aspect of the game. In addition, regular and irregular tasks differed in that participants were to repeat the content of the regular tasks three times when they were encoded whereas participants were free to encode irregular tasks as they wished. Therefore, regular tasks were associated with enhanced encoding relative to irregular tasks.

Individuals with PD demonstrated preserved performance relative to healthy control participants for regular tasks when the cues were focal. However, participants with PD were impaired when the tasks involved less focal or irregular cues. In addition, Rose et al. also found that retrospective memory was nearly perfect for both PD and control groups for the content of the regular tasks, but was significantly reduced in PD for the irregular tasks. Therefore, individuals with PD demonstrated deficits in regular PM despite preserved retrospective memory for the task content. On the other hand, the PM impairments for irregular tasks were also associated with impaired retrospective memory. This pattern suggests that PM deficits in PD may be due to difficulties with encoding the content of the PM tasks, in part, but PM deficits were observed even when retrospective memory was intact. Rose et al. suggested that, in line with Kliegel, Phillips, et al. (2005) and Kliegel, Zimprich, et al. (2005), whether individuals with PD demonstrate PM deficits may be dependent on the intention formation phase. Overall, given that participants showed improved performance for PM tasks when the cues were regular, or more focal nicely demonstrates that lowering strategic, monitoring demands may indeed influence the PM impairment in PD. However, in line with the mediation assumption of the process model proposed earlier, the amount of impairment may depend on the specific match/mismatch between task requirements and patients' resources.

While most studies focussed on event-based PM, Costa et al. (2008a) followed the initial study by Katai and colleagues and investigated event- and time-based PM in PD. Participants were asked to carry out different actions after 20 min had passed (time-based) or after a timer rang (event-based). For the time-based task, individuals could check a clock behind their back for time monitoring. Additionally, all participants completed a broad neuropsychological test battery that assessed declarative memory, short term memory, working memory and executive functions. Opposite to Katai et al., Costa and colleagues found impaired time-based PM and preserved event-based prospective remembering. They concluded that deficits in time-based tasks in PD may be due to their high demands on frontally mediated executive and attentional control processes which are impaired in PD (Einstein, McDaniel, Richardson, Guynn, & Cunfer, 1995; Park et al., 1997). However, findings might be limited by ceiling effects of the event-based task. Moreover, the Costa et al. and the Katai et al. studies differed in the salience of their cues (which directly affects the actual task requirements; perhaps more than the time- versus event-based feature). While cues in the Costa et al. study were rather salient (a timer ring), the cues in the Katai et al. study were embedded in the ongoing task. Hence, both tasks required different retrieval strategies which likely limited their comparability due to those differences in executive task requirements.

Most recently, Raskin et al. (2011) aimed at overcoming those limitations by comparing PD patients' time-based and event-based PM performance in the Memory for Intentions Screening Test (MIST; Raskin, 2009) which includes four tasks of each category that are parallel in structure and delay and that have to be executed in the context of one ongoing activity. Reporting on a remarkably large sample of 54 PD patients and 34 healthy matched control participants, Raskin et al. revealed an interaction between task type and PD status. This interaction reflected a reliable deficit of PD patients in the time-based PM tasks and a non significant trend in the event-based tasks. Thus, results were in line with Costa et al., but in contrast to Katai et al. However, while Raskin et al. elegantly

addressed the differential task structures of time- versus event-based PM that had been limiting the conclusions from the previous literature, Raskin and colleagues' data on event-based PM demonstrated clear ceiling effects (especially in the control group that scored an average of 7.2 out of 8 possible correct PM responses). Hence, the differential pattern of PD effects on time- and event-based PM still awaits confirmation in future studies.

Besides examining PM impairments, both Costa et al. (2008a,b), Costa, Peppe, et al. (2008) and Raskin et al. (2011) also reported detailed analyses on group and individual differences in several facets of cognitive functioning. In both studies, individuals with PD showed reduced performance in the applied neuropsychological tests, mainly with respect to working memory, self-shifting and self-maintaining abilities (Costa et al.) and episodic memory, short-term/working memory, planning, task switching, inhibition and verbal fluency (Raskin et al.). Further analyses in Costa et al. pointed toward a trend of relations between working memory, executive functions and time-based PM in the PD group (similar findings emerged in Raskin et al. where inhibition was a particularly strong predictor for time-based PM). Clock checking behaviour was only assessed by Costa et al. and indicated impaired strategy use in PD patients: Individuals with PD checked the time less often than controls. In terms of underlying neuro-cognitive correlates, they argued that difficulties with time estimation may be related to basal ganglia dysfunction (Koch et al., 2004; Smith, Harper, Gittings, & Abernethy, 2007). Interestingly, in contrast to Katai et al. and Kliegel et al., the PD group showed reduced retrospective memory for the specific PM actions in comparison to controls in both studies (Costa et al. and Raskin et al.). While Raskin et al. argued that this is evidence that, in addition to the prospective component, the retrospective component is also affected in PD, Costa et al. concluded based on patients' clock checking behaviour that general deficits in strategic and attentional processes for encoding and retrieval of intentions rather than intention storage contributed to the PM impairment. Moreover, here, only few patients showed reduced results in the retrospective memory scores of the neurological test battery and there was no unique relation between retrospective memory performance in the neurological tests and in the PM task.

In a second study, Costa et al. (2008a,b) focused on the influence of dopamine on PM performance in PD. Thereby, authors directly targeted the hypothesis that PM impairments may be explained by dysfunctions in fronto-striatal brain structures as a result of dopamine depletion (Cools, 2006; Costa et al., 2003; Lewis et al., 2005; Owen, 2004a,b). Specifically, they argued that the individual dopamine level of patients might affect their PM performance. Importantly, studies have varied regarding their attempts of controlling possible medication effects. Some tested patients after a washout phase (i.e., 12 h after their last medication intake; e.g., Altgassen et al., 2007; Kliegel, Phillips, et al., 2005; Kliegel, Zimprich, et al., 2005); however, possible longstanding drug effects cannot be completely excluded. Others tested patients in "on"-states after having taken their daily medication (e.g., Costa et al., 2008a,b; Costa, Peppe, et al., 2008; Katai et al., 2003). Costa et al. (2008a,b) and Costa, Peppe, et al. (2008) tried to control for potential dopamine influences by testing all patients once in an "on"-state condition and in an "off"-state condition. Participants completed the same time-based PM task as in the Costa et al. (2008a) study. In contrast to Foster et al.'s study, results indicated a positive effect of levodopa on PM performance in PD: Administration of L-dopa improved accuracy of intention retrieval in "on"-patients in comparison to "off"-patients and eliminated performance differences. Further analyses indicated that this improvement did not result from better memory for the intended actions or more strategic time monitoring. The effect was thus interpreted as being due to an increased capacity to create volitional responses, i.e., engage in self-initiated actions (which, however, may be seen as one dimension

of cognitive control/executive functions). In conclusion, arguing that PM depends on intact functioning of the prefrontal lobes (e.g., Simons et al., 2006), the authors hypothesised that the elevated dopamine level in fronto-striatal networks might be the underlying mechanism of enhanced prospective remembering of the medicated patient group.

The impact of dopamine levels on PM performance in PD as a result of medication underlines the earlier claim that disease severity may also be related to PM performance in PD as it determines the integrity of executive functions. Providing some converging support, Whittington et al. (2006) set out to investigate different types of memory (recall, recognition and PM) in PD patients of different disease stages (early stage versus advanced stage). As compared to healthy controls, individuals with PD performed poorer in recall, recognition and in event-based PM tasks. As expected, based on Hoehn and Yahr's (1967) classification, this deficit was stronger for advanced-stage than early-stage PD. Further evidence for the influence of disease severity was provided by Unti et al. (2009) who investigated event-based PM performance in not yet medicated, de novo patients with PD, patients with mild cognitive impairment and healthy adults. Results indicated that de novo patients in an early stage of PD without medication show preserved PM performance as well as almost no cognitive impairments. However two patients with executive dysfunctions also showed impaired prospective remembering.

#### 4. Summary and outlook

In summary, PM research in PD is still in its infancy and several open questions and/or limitations remain. Overall, studies point to a PM deficit in PD. There is strong evidence that this deficit might be due to impaired intention formation as well as self-initiation of intentions. Planning and working memory deficits as well as frontal lobe dysfunctions and dopaminergic changes are discussed as underlying factors on the cognitive and neurobiological level, respectively. However, so far, only a few studies have targeted this directly and future studies are needed to further understand the underlying mechanisms. One hypothesis that we would like to propose in the hopes of stimulating and/or guiding future research is that PM deficits in PD may be largely due to a general impairment in the ability to turn an intention into a series of *actions* – literally, to plan and/or initiate a sequence of motor responses associated with performing a prospective intention. This hypothesis is inspired by Fuster's model of the frontal cortex and the perception–action cycle (e.g., Fuster, 2000). According to Fuster, the frontal cortex is a structure that is largely concerned with *actions*. One of the most consistent results of lesions to frontal cortex is a difficulty with formulating and enacting plans of behavioural, linguistic, or cognitive action. Moreover, the frontal cortex appears to be organized hierarchically, such that primary motor cortex, the lowest level, coordinates simple stimulus–response associations (e.g., *press the button when the light turns on*) that require mapping perceptual input to an appropriate motor response. However, for stimulus–response associations with greater novelty, ambiguity, or complexity, more anterior regions of the frontal cortex are responsible for turning perceptual inputs into appropriate actions that may depend on a variety of rules or contingencies (see also Badre and D'Esposito's (2009) description of a caudal-rostral shift in the hierarchical organization of the frontal cortex).

For example, performing the typical laboratory PM task of pressing one button if a letter string is a word, pressing a second button if it is not, and (rarely) pressing a third button if the letter string is a *particular* word, requires coordinating a series of conditional behaviours that depend upon the particular context of the stimulus. Indeed, Fuster suggests that one of the primary responsibilities of the prefrontal cortex, which sits at the top of the perception–action

cycle, is to mediate contingencies across time by maintaining representations in working memory relevant for the *prospective actions* that are to be performed in the service of a goal. In addition, Fuster (2000, p. 70) suggests that, “as the behaviour becomes automatic (e.g., skilled routines), the action is integrated in lower structures (e.g., premotor cortex, and basal ganglia).” Because of the profile of structural and functional impairments in PD, it is plausible that deficits in PM may largely be the result of impaired processes involved in both planning and initiation of a sequence of conditional motor actions, as well as in turning such actions from controlled to automatic behavioural associations. Indeed, it was recently suggested that the global cognitive dysfunction in PD is the result of a general impairment in the ability to transition from controlled to automatic processing (Koerts et al., 2009). Although these ideas are quite broad in scope, we hope they, along with the conceptual and methodological issues outlined in the first part of this review, might stimulate or guide future research on PM in PD.

Systematic, comparability of the available studies is limited as most studies have been conducted on the basis of different conceptual rationales, and thus have used a broad variety of PM paradigms and manipulations that differed in important task factors. Moreover, different (mostly small) samples of PD patients have been used that differed in their level of ability (due to disease progression, age, medication and individual differences). As outlined above, specific task characteristics may work as potential factors mediating PM performance in PD. Thus, besides large scale studies assessing groups of patients in different disease stages as well as longitudinal studies, systematic model-based delineations of task- and phase-specific predictions are needed. In terms of decomposing factors that affect a PD patient's individual level of ability, the role of concomitant depressive syndromes, general cognitive impairment, and dementia as possible confounds have so far not specifically been addressed. In addition, as there has been no study that directly investigated everyday PM performance, future research should apply more naturalistic paradigms and complement self-ratings with ratings of caregivers to gain an integrated view of PM in PD and explore possibilities to maintain independence for patients.

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