Looking back, thinking ahead
A neuropsychological view on time, space and prospective memory

Neeltje Kant

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A neuropsychological view on time, space
and prospective memory

Terugblikken en vooruitdenken:

een neuropsychologische kijk op tijd, plaats en prospectief geheugen.

(met een samenvatting in het Nederlands)

Proefschrift

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General introduction

"There is one body, but it has many parts. But all its many parts make up one body (…). If one part suffers, every part suffers with it. If one part is honored, every part shares in its joy".

1 Corinthians 12:12&26, NIRV

People rarely consciously think about thinking. We tend to take for granted how our brain works. It seems effortless to be able to drink a cup of coffee, whereas it actually requires highly sophisticated interplay between several processes in the brain to perform such a task (Lezak, 2004). Even more processes are recruited during all the multiple tasks we perform at each moment of the day. Brain functions, like human body parts, are mutually dependent. Only when the system falters, we realize how much we rely on the whole of our body to function. When one part of the body suddenly malfunctions, we experience how often we use it in daily life. I personally suffered from a shoulder injury and found out how crucial this body part is. Apparently you don't only use your hands to write… Likewise, we don't only use our memory to remember. To adequately store new information in memory and retrieve it at the appropriate moment, other cognitive functions are necessary as well, for example visual perception (to process an image to remember), directed attention (to the information to be stored), and mental flexibility to shift focus from one memorable event to another. These functions are all part of complex systems in the brain. Adequate functioning in daily life is determined by the integrity, efficacy and efficiency of these systems. Still, each part plays its own role. Different brain regions are involved in distinctive actions. Even though the foot needs the hand to tie its shoes, both hand and foot have their own separate functions.

In the studies described in this thesis neuropsychological methods were applied to investigate the interplay between multiple cognitive functions, in task situations where adequate cooperation of these functions is needed. Neuropsychologists strive to describe relations between brain and behavior, and attempt to clarify these relations scientifically (Deelman & Eling, 2007). The basis of the discipline of neuropsychology lies in research on functional specialization within the brain, by studying differences in cognitive consequences of selective lesions. The field evolved vastly in the 20th century following the first and second World Wars. Large numbers of injured soldiers with relatively 'clean' missile wounds resulting in focal brain lesions provided a wealth of information on how brain functioning changed when one specific part is damaged (Lezak, 2004). A core method used is that of dissociation of cognitive processes. Whether certain processes are separable can be demonstrated when selective impairments of

those processes occur (Kandel, Schwartz & Jessell, 2000). One of the earliest examples of a double dissociation is the differentiation between language production (A) and comprehension (B), demonstrated by Broca and Wernicke who both described cases with selective damage in different parts of the brain. Where Broca's patients' deficits were confined to the production of language, with intact comprehension (A, not B), Wernicke found the opposite pattern (B, not A). This demonstrates that different brain mechanisms underlie these processes, as they are dissociable. These cases helped to understand language functioning better.

A potential caveat of lesion studies is focusing only on localization. As Hughling Jackson (in Gazzaniga, 2008) stated: while a brain lesion may produce a certain symptom, it does not follow that the injured area is specialized for only that function. Behaviors are constellations of activities, not a single unit. Complex acts are the products of countless neural interactions involving many sites in the neural network; their neuroanatomical correlates are not confined to any specific local area of the brain. Therefore, it is important to describe the effects of brain damage on cognition, to better understand and disentangle human behavior itself. Neuropsychologists these days are not only interested in linking mental activities to brain structures (the *where*), but also in *how* cognitive functions work. The study of dysfunctional behavior can help to identify the component operations that underlie normal cognitive performance. From studying how cognition changes after brain damage, we can gain knowledge on cognitive constructs and on how the brain functions, but also derive information on how to address problems that might occur in brain damaged patients. Moreover, we can apply this knowledge in clinical practice. With this purpose, when I started working as a neuropsychologist in a clinical setting, I also remained active in scientific research. The research projects I worked on and that are described in this thesis all involve the study of function differentiation based upon dissociations and correlations between different cognitive functions.

Another pitfall of dissociation studies is that often rare cases are selected and described, that may not be representative of cognitive functioning in the general population. A preferable method is to investigate how often dissociations occur in groups of patients compared to healthy control participants. In this thesis, groups of patients were studied with different forms of brain damage. The specific characteristics of their pathologies allow for the examination of cognitive function differentiation from multiple perspectives, which complement each other. We derived information on the behavioral consequences of focal (stroke) as well as global (multiple sclerosis, MS) brain damage, in mild (mild cognitive impairment, MCI) and advanced (dementia) stages of cognitive deterioration. By studying the effects of disruptions by each of these conditions, it can

become apparent what underlies certain cognitive constructs and how different functions relate to each other.

A particular cognitive construct that calls for further delineation of its cognitive architecture is prospective memory (PM). PM is the ability to remember intended actions (McDaniel & Einstein, 2011). These actions can be coupled with a certain moment in time, for example when you want to post a card on time for your grandmother's birthday, or with an event, when you try to remember to buy milk on your way home. PM involves thinking ahead (the prospective component, keeping the intention in mind to be executed at the appropriate moment), but also looking back (the retrospective component, to recall what the action was you intended to perform) (Van Den Berg, Kant, & Postma, 2012). Several stages in PM can be discerned: formation of the intention, maintaining it over a delay period, monitoring the appropriate moment for execution, performing the intended action and evaluating the outcome (Glisky, 1996). The multiple different components that constitute PM make apparent that it is a complex construct. It follows logically that adequate interaction between different cognitive functions is necessary to correctly perform a prospective memory task. However, the components involved in PM are not easily incorporated in established theoretical frameworks. Classically, in neuropsychology, cognitive functions are divided into several domains. Commonly distinguished principal domains are memory, language, attention/executive functioning, information processing speed and perception. PM is obviously not restricted to any one of these domains, and it is not easily defined as a separate cognitive function as it seems tightly connected to several other functions. It transcends existing domain and function classifications. Previous research on PM does not provide a clear picture yet of what domains are involved to what extent. Therefore, it is particularly interesting to study how the different parts that are involved in PM interact and how they each play their own role. The majority of the studies described in this thesis are therefore devoted to the investigation of the PM construct.

It is important to understand what cognitive functions are involved in PM, as PM is highly relevant for everyday functioning (Mioni et al., 2013). When people with neurological disorders have memory complaints, these often seem to concern prospective memory failures such as not being able to be on time for appointments, rather than complaining that they cannot remember what they did the day before (retrospective memory). One could expect that PM would have been extensively studied in clinical populations where these problems arise, but, surprisingly, most PM research thus far has been performed in healthy persons. To tailor patient care and to help patients cope with their problems, it is necessary to understand how PM is affected in patients with different pathologies. In the clinic where I work as a neuropsychologist with people

who are often severely affected mostly by neurological conditions, my experience is that the more you know, the more you can do. Often, with use of individually matched compensatory strategies, it is still possible for these people to attain their personal goals.

The first step in this thesis was to collect information on the extent to which PM is affected in relevant clinical populations. To this aim, in **chapter two** we performed a meta-analysis of studies on PM in MCI and dementia. Although these patient groups are known for their memory disorders, there are limited studies available on their PM functioning.

The next chapter (**chapter three**) is dedicated to the investigation of what cognitive functions are involved in different aspects of PM in a group of patients who suffered from a cerebral stroke. These patients comprise an ideal group to study dissociations, as they display focal lesions that can be distributed throughout the brain. The cognitive consequences of stroke depend on what neural networks are disturbed. This heterogeneous group of patients was used to disentangle different aspects of PM. In particular, we aimed to dissociate which cognitive processes are related to event- versus time-based prospective memory (EBPM and TBPM).

Inspired by the results from chapters two and three, a theory driven approach on investigating the cognitive architecture underlying PM was pursued in the next chapter. In **chapter four**, we describe a study in healthy participants using a Bayesian model selection approach on different hypotheses regarding the interaction between several processes thought to be relevant to a different extent for EBPM and TBPM: monitoring behavior, ongoing task performance, verbal and visuospatial attention and working memory, spatial and temporal episodic memory, and time perception. With the Bayesian statistical approach, it is possible to directly compare and evaluate different competing alternative hypotheses. This study generated new questions regarding the processes that were thought to be related to PM, which we further studied in the next chapters.

In **chapter five** we describe dissociations between spatial and temporal order memory, in the same patients who were studied to investigate cognitive correlates of PM (in chapter three). We directly compared retrieval of very recent visual information for spatial location versus temporal order, and binding of these features, to investigate whether these processes are dissociable.

In **chapter six**, cognitive correlates of time perception were investigated, by analyzing correlations between neuropsychological task performance (in the domains of memory, attention/executive functioning and information processing speed) and three task dimensions of time perception: estimation, reproduction and production, as these are thought to be supported by different cognitive processes. Also, as we did in chapters three and five, case study statistical procedures were applied to investigate functional dissociations, comparing individual patients with focal brain damage following stroke.

After studying cognition in stroke patients in order to determine whether functional dissociations occur in patients with focal brain damage, we next investigated a clinical population with a more global network deficiency: patients with advanced MS. In **chapter seven**, we describe which cognitive functions are affected in these patients. Often, in MS research, focus lies on whether cognition is affected and not on how or to what extent different functions are involved. Also, the literature is biased towards MS patients in relatively mild disease stages, and it seemed that the impression derived from literature did not adequately match my own clinical observations. In the clinical setting of Nieuw Unicum, patients reside who are disabled to such an extent that they are not able to live independently, requiring 24/7 care. Their cognitive deficits seemed particularly extensive and debilitating, and included prospective memory problems. We set out to investigate both what functions are affected in advanced MS, and how they interact.

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Remember to buy milk on the way home! A meta-analytic review of prospective memory in mild cognitive impairment and dementia

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Abstract

Prospective memory (PM) is the ability to remember to execute delayed intentions. Previous studies indicate that PM is impaired in persons with mild cognitive impairment (MCI) and dementia, but the extent, nature and cognitive correlates are unclear. A meta-analytic review was therefore performed (literature search 1990-July 2011) on case-control studies on PM in dementia (10 studies, 336 patients, 505 controls) and MCI (7 studies, 225 patients, 253 controls). Differences between event-based and time-based PM and between measures of prospective and retrospective memory were examined, as well as correlations with other cognitive functions. Results showed that patients with dementia or MCI exhibit large deficits in PM (Hedges' d -1.62 [95% confidence interval -1.98 to -1.27, $p < .0001$] for dementia; -1.24 [-1.51 to -0.995, $p < .0001$] for MCI; difference dementia *vs.* MCI: $Q_M = 1.94$, $p = .16$). Impairments were comparable in size for event-based and time-based PM ($p > .05$), as well as for prospective and retrospec-tive memory ($p > .05$). PM showed modest correlations with measures of retrospective memory (median $r = 0.27$) and executive functioning (median $r = 0.30$). PM appears a valid construct in neuropsychological assessment in patients with dementia or MCI, but more insight is needed in the optimal characteristics of PM tasks to be used in clinical practice.

Introduction

Prospective memory (PM) is defined as remembering to carry out intended actions at an appropriate time in the future (McDaniel & Einstein, 2011). It requires multiple cognitive operations, including forming and organizing an intention, remembering the intention over a delay period, monitoring when and how to execute the intention, performing the intention and remembering that is has been carried out (Glisky, 1996). Successful functioning of PM is crucial to independent living in the community (Cockburn & Smith, 1988; Sinnott, 1989). Two distinct components concur in the performance of a typical PM task: (1) a *prospective component* which refers to remembering the intention to perform an action at the appropriate moment without an explicit external prompt and (2) a *retrospective component* in which the specific action to be performed is recalled once the prospective intention to act has been retrieved (Einstein & McDaniel 1990, 1996). A critical difference with retrospective memory (RM), that is, the recollection of past events, is that PM is believed to be more dependent on internal control mechanisms (Craik 1983, 1986). Whereas in RM tasks subjects are prompted by the examiner to initiate retrieval of a certain item, in PM tasks there is no external agent requesting memory search when the target event occurs (McDaniel & Einstein, 2000). PM therefore involves both episodic memory and executive abilities, and thus may rely on multiple neurocognitive systems, most prominently the prefrontal and medial temporal lobe systems (West, 2005; Burgess, Quayle & Frith, 2001).

A distinction has been made between time-based and event-based PM (Einstein & McDaniel, 1990). Event-based PM involves remembering to perform an intended action when a specific event occurs (e.g. remembering to mail a letter when passing a mailbox). Time-based prospective memory involves remembering to perform an intended action at a specified time (e.g. remembering to ring the doctor in the afternoon). It is thought that time-based PM is even more reliant on internal, self-initiated control mechanisms than event-based PM because it is not prompted by an external cue (e.g. the mailbox) (d'Ydewalle, Bouckaert, & Brunfaut, 2001). It may therefore be particularly sensitive to age-related decline (Maylor, 1995; for a review see Henry, MacLeod, Philips, & Crawford, 2004; Uttl, 2008).

Interest in the PM construct began in the 1990s in the field of cognitive psychology and only recently became a relevant topic in the field of clinical neuropsychology. As a consequence, PM has been studied most extensively in healthy persons in laboratory settings (e.g. d'Ydewalle, Luwel, & Brunfaut, 1999). This is surprising since PM complaints are common in clinical neuropsychology (Smith, Della Sala, Logie, & Maylor, 2000) and anecdotal evidence suggests that older persons initially consult their doctors because

of their (relatives') PM rather than RM problems (Camp, Foss, Stevens, & O'Hanlon, 1996). Moreover, adequate PM performance is critical to quality of life (Burgess, 2000) and to a number of daily activities, such as medication adherence and keeping appointments (Einstein, Holland, McDaniel, & Guynn, 1992). One reason for the lack of clinical studies could be difficulty in applying the experimental methods in clinical settings and/or translating these methods into everyday functioning.

Deficits in memory and executive functioning, which are involved in PM, are characteristic features of (Alzheimer's) dementia (Backman, Jones, Berger, Laukka, & Small, 2005; Arnaíz & Almkvist, 2003) and its prodromal stage: mild cognitive impairment (MCI; Arnaíz & Almkvist, 2003; Hodges, 2000; Baddeley, Baddeley, Bucks, & Wilcock, 2001; Petersen, 2004). Both dementia and MCI are, to varying degrees, associated with functional and structural decline of the medial temporal and prefrontal areas in the brain (Bell-McGinty, Lopez, Cidis Meltzer, Scanlon, Whyte, DeKosky, & Becker, 2005; Feldman & Jacova, 2005; Masdeu, Zubieta, & Arbizu, 2005; Scheltens, 2009). Since these cognitive functions and the affected brain structures are central to PM, prominent PM deficits are to be expected in dementia and MCI. Some authors have documented that PM tasks have a higher discriminative power in detecting MCI and dementia than traditional RM measures (Huppert & Beardsal, 1993; Blanco-Campal, Coen, Lawlor, Walsh, & Burke, 2009), thereby suggesting that a deficit in PM might be an early marker of cognitive decline. Surprisingly, evaluation of cognitive deficits in these conditions within the PM framework is still limited. Moreover, in the scarce literature of PM performance in dementia and MCI, several inconsistent findings emerge. For example, some results indicated that patients with dementia showed greater impairment on time-based PM measures as compared with event-based PM measures (Costa et al., 2010), as is found in normal aging (Henry et al., 2004). This effect was, however, not found invariably (Maylor, Smith, Della Sala, & Logie, 2002). Alternatively, it has been suggested that any differential effect on event-based and time-based measures is merely due to differences in task characteristics (Maylor et al., 2002), such as the extent to which a task depends on automatic *vs.* controlled (effortful) processing, rather than the difference in type of cue for action (a particular time or event, respectively). Similarly, while some studies showed greater deficits in PM performance as compared with RM performance in dementia or MCI (Costa, Perri, Serra, Barban, Gatto, Zabberoni, Caltagirone, & Carlesimo, 2010; Blanco-Campal et al. 2009), others show no such effect or even reverse effects (Thompson, Henry, Rendell, Withall, & Brodaty, 2010).

The primary aim of the present meta-analysis was to quantify the nature and extent of PM deficits in MCI and dementia. Firstly, this provides a reliable estimate of the size of PM problems in these conditions, based on the present literature. Secondly, the pro-

posed differences between time-based and event-based PM performance, between prospective and retrospective memory performance and the cognitive correlates of PM performance in MCI and dementia will also be examined in this meta-analysis, in order to provide further insight in the construct validity, as well as the value of PM measures in clinical evaluation of cognitive deficits in these conditions.

Methods

Identification of studies

The aim of this meta-analysis was to include all published studies that provide an estimate of prospective memory performance in patients with MCI or dementia. Studies were selected by means of a MedLine literature search (1990 to 1 July 2011) using the keywords ('prospective memory' or 'prospective remembering' or 'delayed intention') in combination with ('dementia' or 'Alzheimer's disease' or 'mild cognitive impairment') in full or truncated versions. Titles and abstracts were scanned and potentially eligible papers were collected in full-text. Additional studies were identified by examining the list of references of these studies. Several inclusion criteria were applied in order to perform a quantitative analysis: (1) the paper was an original article, (2) prospective memory performance was assessed in both patients and a control group that was matched for demographic variables such as age, gender and level of education, (3) test scores were presented for the patients and the control group (mean and standard deviation), or the exact *p* values, t values, or F values were given. In case of insufficient statistical data an attempt was made to contact the authors. EvdB judged eligible papers according to the inclusion criteria.

Data synthesis and analysis

Effect sizes were calculated for the difference in test scores between patients and control participants. This was done for MCI and dementia separately. The effect size estimate used was Hedges' *d*, that is, the standardized difference between the groups (Hedges & Olkin, 1985). Hedges' *d* was used instead of the more commonly reported Cohen's *d* or Hedges' *g* since it is corrected for a bias due to small sample size (Hedges & Olkin, 1985). The direction of the effect size was negative if the performance of the patient group was worse than the control group. For variables with a non-normal distribution, nonparametric variance estimates were calculated.

In the meta-analysis, an overall *d* value was calculated, expressing the magnitude of associations across studies, weighted for sample size (Hedges & Olkin, 1985). Stouffer's *Z* provided an indication of the significance of the difference in task performance

between the patients and the control group. A 95% confidence interval was calculated based on the standard error. In addition, the overall effect size was used in a random effects model to determine the total heterogeneity of the effect sizes (Q_T) and tested against the χ^2 distribution (with n-1 degrees of freedom; Hedges, 1981). A significant Q_T means that the variance of the effect sizes is greater than to be expected from sampling errors and implies that other explanatory variables should be investigated.

The difference between the overall effect size for MCI *vs.* dementia, for event-based prospective memory (EBPM) *vs.* time-based prospective memory (TBPM) and for PM *vs.* RM was examined with the Q-statistic for heterogeneity. This procedure is analogous to analysis of variance, where one is interested in determining whether or not there is a difference among group means. It is performed by partitioning the total heterogeneity Q_T in Q_M, which is the variation in effect sizes explained by the model, and Q_E which is the residual error variance not explained by the model. Q_M is thus a description of the difference among group cumulative effect sizes and a significant Q_M implies a difference between the overall effect sizes for the groups (Hedges & Olkin, 1985).

The fail-safe number was computed to explore the robustness of the results to the possibility of publication bias. The fail-safe number of studies N_R provides an estimation of how many non-significant or missing studies would be needed to render the observed meta-analytical results non-significant (Rosenthal's method: $a < .05$). All analyses were performed with MetaWin version 2.0 (Rosenberg, Adams, & Gurevitch, 2000).

Data for event-based and time-based prospective memory as well as summary/total scores representing both types of PM were separately included in the analysis. However, when multiple measures of the *same* cognitive construct were provided (e.g. ≥2 EBPM-measures in a single study; Blanco-Campal et al. 2009; Kazui, Matsuda, Hirono, Mori, Miyoshi, Ogino, Tokunaga, Ikejiri, & Takeda, 2005; Huppert & Beardsal, 1993), the effect sizes were averaged to give each construct measured in each study the same weight in the analysis. Duchek, Balota, & Cortese (2006) provided data on 2 different control groups; for this study the effect sizes were averaged. Schmitter-Edgecombe, Woo, & Greeley (2009) provided data on 2 different MCI-groups; for this study the effect sizes were also averaged. One study presented data on activity-based PM, which is defined as a kind of PM in which the target event is represented by finishing an ongoing activity (Schmitter-Edgecombe et al., 2009). Because data on activity-based was limited and it is in many ways similar to EBPM (Kvavilashivili & Ellis, 1996), this measure was incorporated as EBPM in the present meta-analysis (see also Brewer, Marsh, Clark-Foos, Meeks, Cook, & Hicks, 2011). When reported, measures of RM were also extracted from the included

studies. Separate analyses were performed for RM measures that were *unrelated* to the PM task and RM measures that were *part of* the PM task.

This meta-analysis was performed in 4 consecutive steps. First, overall effect sizes for dementia *vs.* controls and MCI *vs.* controls were calculated and compared between dementia and MCI. Second, overall effect sizes for time-based and event-based PM were calculated and compared within and between both patient groups. Third, overall effect sizes for prospective and retrospective memory measures were calculated and compared within and between both patient groups. Finally, correlational data were summarized from studies that examined the association between PM measures and other neuropsychological measures.

Results

The literature search yielded 35 hits, 15 of which considered one or more measures of prospective memory in patients with MCI or dementia (excluded studies: 4 reviews; 9 did not include a control group, investigated other patients groups [e.g. Down's syndrome, Parkinson] or only healthy persons; 3 investigated the effect of an intervention to improve prospective memory; 4 examined subjective complaints or used a questionnaire as a measure of prospective memory). After examination of the reference lists one more eligible study was added (Huppert, Johnson, & Nickson, 2000). Three studies were subsequently excluded because of insufficient statistical data provided (Livner, Laukka, Karlsson, & Bäckman, 2009; Huppert et al., 2000) or lack of formal testing of prospective memory (Anderson & Schmitter-Edgecombe, 2010), leaving 13 studies in the present analysis. Tables 1 and 2 display the characteristics of the included studies for dementia and MCI separately. Two studies provided data on both dementia and MCI (Thompson et al.. 2010; Troyer & Murphy, 2007) and were thus included in both tables.

Seven of the 13 included studies used laboratory-based PM tasks (Kinsella, Ong, Storey, Wallace, & Hester, 2007; Troyer & Murphy, 2007, Duchek, Balota, & Cortese, 2006; Maylor et al., 2002; Schmitter-Edgecombe et al., 2009, Blanco-Campal et al., 2009, Karantzoulis, Troyer, & Rich, 2009). These tasks typically involve an ongoing cognitive exercise (e.g. making puzzles, reading sentences or watching a film) during which a specific event occurred (a target stimulus or expiration or a certain time-period), after which a specified action should be performed (e.g. name target animal, ask for a colored pen). The other 6 studies used PM tasks that resembled more naturalistic situations that could occur in normal daily living. For example, the prospective subtasks of the Rivermead Behavioral Memory Test (i.e. ask for a belonging, remind examiner that he or she has

Table 1 Summary of studies included in the meta-analysis: Dementia

	n		age		Gender (% male)		Education (years)		MMSE		Dementia diagnosis	PM type	PM task description	*d*
Study (year)	**D**	**C**	**D**	**C**	**D**	**C**	**D**	**C**	**D**	**C**				
Thompson et al. (2010)	39	53	79.8±6.2	77.8±4.7	51	42	12.0±4.5	11.3±3.3	25.3±4.3	28.7±1.4	DSM–IV	PM	'Virtual Week', perform 4 tasks per day over 2 days	-1.46
												EBPM	- when event occurs	-0.60
												TBPM	- at a specific time	-1.19
Martins et al. (2008)	20	20	75.6±7.8	74.1±6.8	45	45	5.6±4.5	5.8±4.4	22.6±1.9	29.0±1.3	NINCDS/ ADRDA, DSM–IV	PM	RBMT + target animal, remind examiner in 5 min.	-2.35
Mori et al. (2007)	52	50	81.2±5.3	80.0±5.0	0	0	9.1±1.9	8.9±1.8	17.6±4.1	27.2±2.2	Not specified	EBMP	RBMT total PM score	-1.05
Kinsella et al. (2007)	14	14	79.1±6.2	75.7±4.2	36	36	11.0±3.5	11.6±3.0	23.3±3.0	28.9±1.5	NINCDS/ ADRDA	EBPM	Substitute target word in text-reading task	-1.99
Troyer et al. (2007)	45	42	78.4±5.6	75.1±6.4	58	41	12.5±2.4	13.8±3.3	25.5±2.2	28.7±1.2	NINCDS/ ADRDA		During cognitive testing:	
												EBPM	Use colored pen in task requiring writing	-1.72
												TBPM	Report time every 30 min.	-1.86
Duchek et al. (2006)	27	20	78.0±7.5	72.5±3.4	-	-	14.2±3.2	14.5±2.7	-	-	NINCDS/ ADRDA	EBPM	Respond to target word in general knowledge test	-2.22
									13	86.8±4.8	-	15.0±4.0	-	-1.10
Jones et al. (2006)	46	188	84.0±4.9	84.0±5.2	-	-	8.2±2.4	8.9±2.8	24.4±2.8	27.1±2.2	DSM–III–R	EBPM	Remind test leader to make phone call (+cue)	-0.60
Kazui et al. (2005)	48	48	67.7±8.5	66.7±9.4	37.5	37.5	11.4±2.2	11.5±2.5	21.9±2.3	28.2±1.8	NINCDS/ ADRDA	EBPM	RBMT	
													Belonging	-4.18
													Appointment	-1.71
													Message (immediate)	-1.57
													Message (delay)	-1.6

Table 1 Summary of studies included in the meta-analysis: Dementia (continued)

	n		age		Gender (% male)		Education (years)		MMSE		Dementia diagnosis	PM type	PM task description	*d*
Study (year)	**D**	**C**	**D**	**C**	**D**	**C**	**D**	**C**	**D**	**C**				
Maylor et al. (2002)	24	30	68.5±8.0	67.3±4.2	-	-	10.1±2.1	12.3±3.6	22.1±3.6	-	Spinnler (1988)		Watch film	
												EBPM	Name animal target	-0.28
												TBPM	Indicate 3 minutes	-1.95
Huppert et al. (1993)	12 min. AD	27	87.3 (77-92)	81.1 (76-86)	42	37	14.5 age left school	14.5 age left school	19.8 (12-25)	24.8 (22-30)	MMSE, CAMCOG	EBPM	RBMT	
													Belonging	-2.20
													Appointment	-2.07
													Message (immediate)	-2.14
													Message (delay)	-1.89
	9 mod. AD	27	80.6 (70.86)	81.1 (76-86)	33	37	14.1 age left school	14.5 age left school	15.3 (7-23)	24.8 (22-30)	MMSE, CAMCOG	EBPM	RBMT	
													Belonging	-2.49
													Appointment	-3.27
													Message (immediate)	-2.17
													Message (delay)	-2.22

Note. D, dementia; C, control group; MMSE, Mini Mental State Examination; EBPM, Event-based prospective memory; TBPM, Time-based prospective memory; PM, prospective memory summary score; RMBT, Rivermead Behavioral Memory Test; CAMCOG, cognitive part of the Cambridge examination for mental disorders of the elderly; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association; SM-III-R/DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, revised 3rd edition/4th edition.

Table 2 Summary of studies included in the meta-analysis: MCI

Study (year)	n		age		Gender (% male)		Education (years)		MMSE		MCI diagnosis	PM type	PM task description	*d*
	MCI	C	MCI	C	MCI	C	MCI	C	MCI	C				
Costa et al. (2010)	20	20	72.2±5.9	71.5±6.1	40	55	10.3±3.7	10.5±4.8	26.0±1.4	28.2±1.4	Petersen (2004)	EBPM	Six triplets of actions	-1.21
												TBPM	Six triplets of actions	-2.24
Thompson et al. (2010)	48	53	78.6±4.9	77.8±4.7	54	42	12.2±3.9	11.3±3.3	28.0±1.6	28.7±1.4	Petersen (2007)	PM	'Virtual Week', perform 4 tasks per day over 2 days	-0.77
												EBPM	- when event occurs	-1.20
												TBPM	- at a specific time	-0.70
Schmitter-Edgecombe et al. (2009)	27 aMCI	42	71.3 (52-91)	72.5 (50-92)	48	40	16.1 (12-20)	16.1 (11-20)	26.9 (24-30)	28.7 (26-30)	Petersen (2001)	EBPM[+]	During cognitive testing: Ask examiner for pill bottle after every task	-1.63
									15 naMCI	72.2 (48-95)	27	15.9 (12-20)	27.4 (24-30)	-1.10
Blanco-Campal et al. (2009)	19	21	71.15±5.6	72.5±5.6	47	29	3: > 13y 16: ≤ 13y	8: > 13y 13: ≤ 13y	25.7±2.0	29.4±0.7	Portet (2006)	EBPM	'Silly sentences'	
													Non-specific target	-2.53
													Specific target	-1.27
Karantzoulis et al. (2009)	27	27	75.7±7.6	73.0±5.9	44	26	13.0±3.5	14.2±3.1	-	-	Petersen (2004)	PM	MIST during word puzzle	-1.48
												EBPM	e.g. 'rewind a tape'	-0.70
												TBPM	e.g. 'take break after 2 m'	-1.21
Troyer et al. (2007)	45	42	75.8±6.7	75.1±6.4	53	41	13.6±3.3	13.8±3.3	27.8±1.4	28.7±1.2	Petersen (2004)		During cognitive testing:	
												EBPM	Use colored pen in task requiring writing	-0.67
												TBPM	Report time every 30 min.	-1.08

Table 2 Summary of studies included in the meta-analysis: MCI (continued)

Study (year)	n		age		Gender (% male)		Education (years)		MMSE		MCI diagnosis	PM type	PM task description	*d*
Kazui et al. (2005)	24	48	66.9±9.4	66.7±9.4	37.5	37.5	11.5±2.6	11.5±2.5	26.7±1.9	28.2±1.8	Petersen (1995)	EBPM	RBMT	
													Belonging	-2.26
													Appointment	-2.56
													Message (immediate)	-0.27
													Message (delay)	-1.84

Note. MCI, mild cognitive impairment; C, control group; MMSE, Mini Mental State Examination; EBPM, Event-based prospective memory; TBPM, Time-based prospective memory; PM, prospective memory summary score; RMBT, Rivermead Behavioral Memory Test; aMCI, amnestic MCI; naMCI, nonamnestic MCI; MIST, memory for intentions screening test; [+] activity-based task = a kind of EBPM in which the target event is represented by finishing an ongoing activity

an appointment and remembering to deliver a message after walking a route; Wilson, Cockburn, & Baddeley, 1985) were administered in several studies (Mori & Sugimura, 2007, Kazui et al., 2005, Huppert, & Beardsall, 1993). EBPM tasks were administered more frequently than TBPM tasks.

Prospective memory performance in patients with dementia or MCI

For dementia, a total of 336 patients and 505 control participants from 10 studies were included in the meta-analysis (Table 1). All but two studies on persons with dementia specifically included patients with Alzheimer's disease (AD). Thompson et al. (2010) and Huppert & Beardsall (1993) did not explicitly specify the dementia type. The overall weighted effect size for patients *vs.* controls was -1.62 (95% confidence interval -1.98 to -1.27, z = 20.32, $p < .0001$). For MCI a total of 225 patients and 253 control participants from 7 studies were included in the meta-analysis (Table 2). All MCI-studies included patients with amnestic type MCI. Schmitter-Edgecombe et al. (2009) and Costa et al. (2010) also included non-amnestic MCI and dysexecutive MCI, respectively. The overall weighted effect size for patients *vs.* controls was -1.24 (-1.51 to -0.995, z = 16.92, $p < .0001$).

According to the nomenclature of Cohen (1988), these effect sizes indicate a large difference ($d > 0.80$) between the patients and the control participants for both dementia and MCI. The test for heterogeneity was not significant (dementia studies $Q_T = 10.58$, $p = .57$, MCI studies $Q_T = 10.68$, $p = .38$), implying that the variance among the effect sizes was not greater than expected by sampling error.

The fail-safe number of studies was 320.3 for the dementia results and 313.3 for the MCI results, indicating that at least 320 and 313 unpublished null-findings were needed to render the effects on prospective memory statistically non-significant. It is unlikely that such a large number of unpublished studies with null effects relative to published studies exist.

Despite a trend towards a larger effect size for dementia ($d = -1.62$) compared with MCI ($d = -1.24$), the confidence intervals of both estimates show considerable overlap, and the Q-statistic (using study type as a categorical moderator) indeed showed that the effects were homogeneous ($Q_M = 1.94$, $p = .16$), indicating no statistically significant difference between the overall effect sizes for dementia and MCI.

Event-based and time-based prospective memory

For dementia, EBPM was assessed in 9 studies with an overall effect size of -1.48 (-1.90 to -1.06, z = 17.87, $p < .0001$). TBPM was assessed in 3 studies with an overall effect size

of -1.42 (-1.95 to -0.60, z = 8.53, $p < .0001$). For MCI, EBPM was assessed in 7 studies with an overall effect size of -1.13 (-1.48 to -0.82, z = 15.80, $p < .0001$). TBPM was assessed in 4 studies with an overall effect size of -1.34 (-1.85 to -1.14, z = 9.03, $p < .0001$). Again, these effect sizes indicate a large difference between patients and control participants for both dementia and MCI. Despite a trend towards larger effect sizes for the TBPM measures in the MCI studies (see Table 2), the effect sizes for EBPM and TBPM were homogeneous, thereby indicating no statistically significant difference between EBPM and TBPM measures, neither when the dementia and MCI studies were taken together ($Q_M = 0.05$, $p = .83$), nor in the dementia ($Q_M = 0.02$, $p = .88$) and MCI studies ($Q_M = 0.64$, $p = .42$) separately, possibly due to the relatively small number of TBPM measures available.

Relation between measures of prospective and retrospective memory

As PM is considered to be related to RM, and PM tasks generally have both a retrospective and a prospective component, the relation between PM and RM was investigated in two ways. First, 11 studies reported results of separate measures of retrospective memory in their study samples. The items that were to be recalled or recognized in the RM tasks were unrelated to the PM task. Table 3 shows the effect sizes for both the PM and the RM measures that were extracted from those studies. For dementia *vs.* controls this resulted in an overall effect size of -1.66 (95% CI -2.08 to -1.23) for the measures of prospective memory and -1.76 (-2.14 to -1.39) for the measures of retrospective memory. The difference between these two overall effect sizes was not statistically significant ($Q_M = 0.11$, $p = .74$). For MCI *vs.* controls the overall effect sizes for prospective and retrospective memory were also similar (prospective -1.41 (-1.72 to -1.11); retrospective -1.10 (-1.27 to -0.85), $Q_M = 1.69$, $p = .19$). In two studies (Troyer & Murphy, 2007; Karantzoulis et al., 2009), the retrospective measures were used in the diagnosis of MCI and dementia, possibly resulting in a bias towards worse performance on the retrospective memory measures. However, exclusion of these studies did not notably alter the results (data not shown). Also, when taking dementia and MCI-studies together, the difference between the overall effect sizes for PM and RM was not statistically significant ($Q_M = 0.05$, $p = .83$).

Table 3 Prospective and retrospective memory performance

	Prospective Memory		Retrospective Memory		Difference	
	Effect size *d*	**variance**	**Effect size *d***	**variance**		
Dementia vs. control						
Kazui et al. (2005)	-2.23	0.07	-2.04	0.06		
Maylor et al. (2002)	-1.09	0.19	-1.46	0.10		
Mori et al. (2007)	-1.05	0.04	-2.42	0.07		
Duchek et al. (2006)	-1.65	0.13	-1.22	0.13		
Jones et al. (2006)	-0.60	0.03	-0.92	0.03		
Troyer et al. (2007)*	-1.79	0.09	-1.96	0.11		
Martins et al. (2008)	-2.35	0.17	-2.52	0.18		
Huppert et al. (2003)						
– minimal dementia	-2.07	0.18	-1.17	0.14		
– moderate dementia	-2.48	0.24	-2.39	0.24		
Overall effect size	-1.66	0.13	-1.76	0.12	Q_M= 0.11	p = .74
MCI vs. control						
Blanco-Campal et al. (2009)	-1.88	0.15	-1.19	0.12		
Kazui et al. (2005)	-1.72	0.09	-1.31	0.08		
Troyer et al. (2007)	-0.88	0.05	-1.14	0.06		
Schmitter-Edgecombe et al. (2009)	-1.38	0.09	-0.64	0.08		
Karantzoulis et al. (2009)*	-1.48	0.09	-1.26	0.09		
Overall effect size	-1.41	0.09	-1.10	0.09	Q_M = 1.69	p = .19

Note. *RM measures used in diagnostic process.

Second, six studies presented a separate analysis on the prospective and retrospective component *within* their measure of prospective memory (Dementia: Maylor et al., 2002; Jones, Livner, & Bäckman, 2006; Thompson et al., 2010; Huppert & Beardsall, 1993; MCI: Costa et al., 2010, Thompson et al., 2010; Karantzoulis et al., 2009). Effect sizes could be calculated from four of these studies to examine the difference between patients and controls in the prospective and retrospective components (Maylor et al., 2002; Costa et al., 2010; Thompson et al., 2010; Karantzoulis et al., 2009). These effect sizes were either calculated from the difference between the retrospective component and total PM performance (Maylor et al., 2002; Thompson et al., 2010) or from the difference between the prospective and retrospective components within the task (Costa et al., 2010; Karantzoulis et al., 2009). The overall effect size (dementia and MCI-studies taken together) was -1.51 (-2.09 to -0.99) for the prospective component and -1.38 (-2.05 to -0.82) for the retrospective component (difference: Q_M = 0.07, p = .79). Of the two studies that could not be included in the effect size calculation, one showed no difference

between the prospective and retrospective component in patients with dementia (Jones et al., 2006); the other showed a significant difference between persons with dementia and controls in the prospective component even when adjusting for the retrospective component in analysis of covariance (Huppert & Beardsall, 1993).

Correlations between PM performance and other neuropsychological tests

Four studies on dementia and seven studies on MCI provided correlation analyses between measures of prospective memory and other neuropsychological test measures (Table 4). Due to considerable variability in chosen measures and analyses a formal meta-analysis was not performed, but a descriptive analysis of these data is presented below. Measures of memory and executive functioning were primarily used in the correlation analyses. A small number of studies also provided data on working memory, attention, processing speed and perception. Overall, the correlation coefficients were small to moderate in size, ranging from -0.22 to 0.72 (median r = 0.27, interquartile range 0.12 to 0.43), a third of which reached statistical significance. The correlations appeared stronger within the patient groups than within the controls. All eight studies explicitly hypothesized significant correlations with retrospective memory and executive functioning, thereby supporting convergent validity of the PM construct. In six out of eight of these studies this hypothesis was (partly) confirmed (median r = 0.27 for memory, median r = 0.30 for executive functioning).

Table 4 Correlations between prospective memory and other neuropsychological tests

		Correlation with Prospective memory		
Test	**Study**	**Control group**	**MCI patients**	**Dementia patients**
Memory				
Word list immediate recall	Costa et al. (2009)		0.38**	
Word list delayed recall	Costa et al. (2009)		ns	
Short story immediate recall	Costa et al. (2009)		ns	
Short story delayed recall	Costa et al. (2009)		ns	
RAVLT total trial 1-5	Schmitter-Edgecombe et al. (2009)	ns	>0.45**	
RAVLT immediate delay	Schmitter-Edgecombe et al. (2009)	ns	>0.45**	
RAVLT long delay	Schmitter-Edgecombe et al. (2009)	ns	>0.45**	
RAVLT total trial 1-5	Martins et al. (2008)			not specified
Recall of 6 object	Huppert et al. (1993)	0.08; 0.18; -0.06; -0.1[d]		0.19; 0.28; 0; 0.36[d]
Free recall of words	Huppert et al. (1993)	0.07; 0.16; 0.13; 0.04[d]		0.61**; 0.58**; 0.34; 0.17[d]
Route – immediate recall	Huppert et al. (1993)	0.22; 0.22; 0.4; 0.29[d]		0.36; 0.51*; 0.39; 0.17[d]
Route – delayed recall	Huppert et al. (1993)	0.11; 0.34; -0.03; 0.44*[d]		0.61**; 0.24; 0.29; 0.42[d]
Recall of name	Huppert et al. (1993)	-0.16; 0.27; -0.22; 0.46*[d]		0.24; 0.17; 0.16; -0.08[d]
HVLT immediate recall	Troyer et al. (2007)[b]		0.48**	0.48**
BVMT immediate recall	Troyer et al. (2007)[b]		0.34**	0.34**
Working memory				
Visual span	Thompson et al. (2010)[b]		0.49**	0.49**
Letter-Number Sequencing (WAIS-III)	Schmitter-Edgecombe et al. (2009)	ns	ns	
Digit Span backward (WAIS-III)	Martins et al. (2008)			-0.02
Executive functioning				
MCST (categories)	Costa et al. (2009)		0.33*	

Table 4 Correlations between prospective memory and other neuropsychological tests (continued)

		Correlation with Prospective memory		
Test	**Study**	**Control group**	**MCI patients**	**Dementia patients**
MCST (perseverative errors)	Costa et al. (2009)		ns	
Word fluency	Costa et al. (2009)		ns	
Trailmaking Test – Part B[a]	Duchek et al. (2006)	Group 1: -0.72**		
		Group 2: 0.004		
Trailmaking Test – Part B[a]	Troyer et al. (2007)[b]		-0.47**	-0.47**
Trailmaking Test – Part B[a]	Martins et al. (2008)			0.09
Trailmaking Test – Part B[a]	Schmitter-Edgecombe et al. (2009)	ns	-0.51**	
D-KEFS design fluency	Schmitter-Edgecombe et al. (2009)	ns	0.43**	
D-KEFS letter fluency	Schmitter-Edgecombe et al. (2009)	ns	ns	
Composite score[c]	Karantzoulis et al. (2009)	0.30	0.21	
Tower of London	Thompson et al. (2010)[b]		0.27**	0.27**
Attention				
Digit Span forward (WAIS-III)	Martins et al. (2008)			-0.10
Processing speed				
SDMT	Schmitter-Edgecombe et al. (2009)	ns	ns	
Trailmaking Test – Part A[a]	Martins et al. (2008)			-0.23
Perception				
Visual perception	Martins et al. (2008)			-0.07

Note. Data are unadjusted pearson or spearman (rank) correlation coefficient extracted from the studies. No meta-analysis was performed.
ns, not significant; [a] Higher score reflects worse performance; [b] Troyer et al. and Thompson et al. present correlation coefficients for MCI and dementia combined, these are presented in both columns; [c] composite score for executive functioning consisting of MCST, word fluency, WAIS-III Arithmetic, Wechsler Memory Scale-Mental Control, WAIS-III Digit Span backward; [d] Huppert et al. presented correlation coefficients for RMBT appointment, belonging and immediate & delayed recall of a message; MCST, Modified Card Sorting Test; HVLT, Hopkins Verbal Learning Test; BVMT, Brief Visuospatial Memory Test; RAVLT, Rey Auditory Verbal Learning Test; WAIS-III, Wechsler Adult Intelligence Scale 3rd Edition; SDMT, Symbol Digit Modalities Test; *$p < .05$ **$p < .01$ ***$p < .001$

Discussion

The present study involved a meta-analytic review of prospective memory in patients with dementia or mild cognitive impairment (MCI), to explore the extent, nature and cognitive correlates of PM in these patients. The results of the meta-analysis, which incorporated 13 studies in total, showed large deficits in PM in both patient groups (Hedges' *d* -1.62 for dementia, -1.24 for MCI), compared with control participants. There was no statistically significant difference in effect sizes between MCI and dementia. To further characterize the nature of these deficits, several contrasts that were proposed in the current literature were tested statistically. These secondary analyses revealed no significant differences between time-based prospective memory (TBPM) and event-based prospective memory (EBPM) (*d* -1.42 *vs.* -1.48 for dementia and -1.34 *vs.* -1.13 for MCI), or between prospective and retrospective memory (components) (*d* -1.66 *vs.* -1.76). Correlation analysis showed significant associations between PM performance and measures of RM and executive functioning. Weak correlations were also observed for working memory and attention, but as these cognitive domains were scarcely examined, strong conclusions about the specificity of these relations cannot be drawn.

Interest in the PM concept in patients with AD or MCI is increasing. This is not surprising since the cognitive functions and brain areas that are typically affected in these conditions (Backman et al., 2005; Arnaíz & Almkvist, 2003; Hodges, 2000; Baddeley et al., 2001; Bell-McGinty et al., 2005; Feldman & Jacova, 2005; Masdeu et al., 2005; Scheltens, 2009) are also involved in PM performance. The finding that the effect sizes in MCI were large and, more importantly, similar in size to those found in dementia corroborates earlier suggestions that PM is already affected in the early stages of the disease (Huppert & Beardsal, 1993). For some other conjectures in the current PM literature no clear support was found in the present meta-analysis. Some authors propose that PM tasks add additional discriminative power in the detection of dementia, above and beyond known psychometric tests for RM (Duchek et al., 2006; Huppert & Beardsall et al., 1993). This suggestion was not corroborated by the present meta-analysis, which showed that the difference in PM and RM performance between patients and controls was rather similar in size. Whereas this might be somewhat surprising, the large effects of dementia and MCI on PM that were demonstrated in the present meta-analysis strongly suggest that PM measures should be part of neuropsychological assessment in clinical practice. As yet it remains to be evaluated what characterizes a valid and reliable measure of PM in clinical populations. Many PM tasks that can be used in clinical populations have

a restricted range of scores that can be obtained (one either remembers to remind the experimenter, or one does not), which may cause limited statistical sensitivity (for a review of methodological issues, see Costa et al., 2010). In addition, studies in healthy participants show effects of the nature and importance of the ongoing task on PM performance (e.g. d'Ydewalle et al., (1999), which is particularly relevant since in clinical practice, PM tasks are typically part of a larger neuropsychological test battery. The effect sizes of the six studies in the present meta-analysis that used naturalistic PM measurement tended to be slightly smaller than those found in studies that used laboratory-based measures, but whether this reflects a true difference or rather results from differences in task characteristics remains to be evaluated.

Several authors proposed a larger effect of (pathological) aging on time-based measures as compared with event-based measures of PM, because the former places a greater burden on internal control mechanisms (Henry et al., 2004). A trend towards a greater effect size for TBPM than for EBPM was indeed observed for MCI, but the difference between the effect sizes did not reach statistical significance for either MCI or dementia. The absence of statistical significance could be, at least in part, due to the relatively limited number of studies that examined TBPM. However, alternative explanations should be considered as well. For one, the observed results raise important questions about the true difference in nature of event-based and time-based PM. Should these concepts be viewed as theoretically different, or is it better to explain reported differences in PM performance in terms of differences in task characteristics? In their multiprocess framework, McDaniel et al. (2004) propose that PM performance may rely on both strategic monitoring and automatic retrieval processes. Based on this premise one may argue that both time- and event-based tasks can vary in the amount of self-initiated activity required or environmental support available. As such, certain EBPM tasks may be more demanding than some TBPM tasks and the reported differences in performance between PM tasks may thus be determined by the extent to which the task depends on automatic *vs.* controlled (effortful) processing, rather than by a difference in type of cue for action (a particular time or event, respectively). This hierarchical viewpoint could provide a more valid explanation for differences in PM performance than the simple distinction between TBPM and EBPM. It should be noted that in the review by Henry et al. (2004), on which many authors have based the hypothesized difference between TBPM and EBPM, a significant difference was indeed *only* observed between conditions with high demand TBPM and low demand EBPM.

The results of the present meta-analysis that indicate that patients with MCI and dementia are equally impaired in time-based and event-based PM, seems to be most in line with a difference in terms of task demands. A recent meta-analytic review in pa-

tients with schizophrenia did reveal a greater impairment in TBPM than in EBPM (Wang, Cui, Chan, Denk, Shi, Hong, Li, Yu, Gong, & Shum, 2009), but it should be noted that the overall effect sizes, particularly those for EBPM, were considerably smaller, probably reflecting a greater overall memory deficit in patients with MCI or dementia compared with patients with schizophrenia. More specifically, the impaired PM performance observed in MCI or dementia may, at least in part, be explained by the presence of a RM deficit in these patients. Indeed, a recent study by Costa et al. (2011), in which executive load was manipulated experimentally, showed that reduced performance on the PM tasks was at least partially underlain by their inability to remember the target words. Thompson et al. (2010) illustrate this possible effect of disease severity by arguing that the difference between TBPM and EBPM is present in patients with MCI, but is no longer visible once patients progress towards dementia. Recent experimental studies increasingly consider the dimensions of focality and regularity in PM (e.g. Rose, Rendell, McDaniel, Aberle, & Kliegel, 2010), but these concepts were not commonly examined in the patient studies included in the present meta-analysis. Therefore, these dimensions were not considered here.

As an indication of construct validity, correlations with tests measuring memory, executive functioning and other cognitive domains were examined. The observed significant correlations between PM and measures of RM and executive functioning indicate adequate convergent validity of the PM construct. However, correlations with other cognitive functions, such as fluid intelligence and perceptual speed, are similar in size (Salthouse, Berish,& Siedlecki, 2004), which is inconsistent with discriminant validity of the PM construct, at least in dementia and MCI. Also, secondary analysis indicated no significant difference between the effect size for the MMSE score and the PM measures (-1,68 [-2,11 to -1,26] *vs.* -1,48 [-1,90 to -1,06], $Q_M = 0.53$, $p = .47$ from 5 studies for MCI, 7 for dementia) although one should keep in mind that MMSE was not included as an outcome measure in any of the studies. Since the present review included only case-control studies in which samples of patients were compared with healthy persons matched for age, gender and educational level, the effect of these demographics on PM was not specifically examined. One would expect that demographics, age in particular, are related to PM performance as is also indicated in a previous review (Henry et al., 2004). Detailed analysis of the impact of gender and level of education would further increase insight in the PM construct.

Strengths of the present study include the use of a meta-analytical approach that provides a weighted estimate of the magnitude of the effects. A limitation concerns the heterogeneity of the included studies with regard to sample size and characteristics of the PM tasks. Also, some of the secondary analyses included a relatively small number

of studies. Finally, the vast majority of included studies was performed in patients with Alzheimer's disease. Whether these finding can be extrapolated to other types of dementia remains to be evaluated.

In sum, the present meta-analysis shows a large deficit in PM in patients with dementia or MCI compared with healthy controls. PM performance was also associated with measures of RM and executive functioning. These impairments were comparable in size for TBPM and EBPM as well as for PM and RM in general. PM appears a valid construct in neuropsychological assessment in patients with dementia or MCI, but more insight is needed in the optimal characteristics of PM tasks to be used in clinical practice.

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Functional correlates of prospective memory in stroke

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Abstract

Introduction: Prospective memory is the ability to remember actions to be performed later in time or when a certain event occurs. Multiple cognitive processes are involved in prospective memory, and the degree to which automatic or effortful processes are involved may differ for different types of prospective memory tasks. This study aimed to investigate prospective memory (dys)functioning in stroke patients, and to get more insight in which cognitive processes are involved in time- versus event-based prospective memory.

Methods: We investigated 39 community-dwelling stroke survivors and 53 matched control participants. Assessment included naturalistic and experimental event- and time-based prospective memory tasks, as well as standard neuropsychological measures of (retrospective) memory, processing speed and attention/executive functioning.

Results: 41% of the stroke patients performed significantly worse than control participants on prospective memory tasks. Deficits in prospective memory occurred as frequently as impairments in retrospective memory (33%, $\chi^2(1, N = 39)= 3.4, p = .066$), and more often than impairments in attention/executive functioning (15%, $\chi^2(1, N = 39) = 5.2, p = .022$) and speed of processing (23%, $\chi^2(1, N = 39) = 6.5, p = .011$). Regression analyses showed that event-based ('focal') prospective memory is supported by retrospective memory, indicating that it is a relatively simple and automatic process. Time-based (non-'focal') prospective memory proved to be a more complex process, requiring active monitoring of the environment. Performance was predicted by speed of processing, attention/executive functioning and retrospective memory. Thirteen percent of the patients suffered from selective prospective memory impairment, which was associated with damage to the superior temporal gyrus.

Conclusions: Impairment of prospective memory occurs frequently after stroke. Different cognitive operations are involved in distinct types of prospective memory. Results fit within the multi-process framework of prospective memory and help further specify its contents.

Introduction

Prospective memory (PM) is the ability to remember intended actions (Einstein & McDaniel, 1990), for example posting a card for your grandmother's birthday. A distinction is often made between event-based and time-based PM (Kliegel, Altgassen, Hering, & Rose, 2011). In event-based PM the intended action is coupled with a specific cue event, as in remembering to tell the latest gossip upon meeting a friend. Time-based PM involves actions to be performed at a certain moment in time, like making an important phone call Monday morning.

Several authors have described the cognitive complexity of PM (e.g. Carlesimo & Costa, 2011). Einstein and McDaniel proposed a multi-process framework in which separate processes of intention-formation, retention, initiation and execution are distinguished (Einstein & McDaniel, 1990; Rose, Rendell, McDaniel, Aberle, & Kliegel, 2010). Research in healthy participants regarding the cognitive functions involved in PM indicates that attention, memory and executive functioning are important for adequate PM performance (Burgess & Shallice, 1997; Marsh & Hicks, 1998; Mioni, Rendell, Henry, Cantagallo, & Stablum, 2013; Otani et al., 1997). There is evidence that (pre)frontal, parietal and medial temporal brain regions are involved (Burgess, Gonen-Yaacovi, & Volle, 2011; Gordon, Shelton, Bugg, McDaniel, & Head, 2011; Martin et al., 2007; West & Krompinger, 2005).

PM deficits have been reported in patients with different neurological problems, such as Parkinson's disease, closed head injury, mild cognitive impairment and dementia (Costa, Peppe, Caltagirone, & Carlesimo, 2008; Kliegel, et al., 2011; Shum, Levin, & Chan, 2011; van den Berg, Kant, & Postma, 2012). PM failure has significant impact on daily life functioning (Mioni et al., 2013). Not surprisingly, patients more often complain about prospective than about retrospective memory (Baddeley, 1990).

As stroke often leads to chronic cognitive deficits and dependency on support (Appelros, Nydevik, & Viitanen, 2003; de Haan, Nys, & van Zandvoort, 2006), deficits in PM potentially play a pivotal role in many of the problems that stroke patients are faced with. As such, one might expect PM to be a main (sub)field of investigation in stroke patients, but until now there is limited knowledge about PM deficits in stroke. Brooks, Rose, Potter, Jayawardena, and Morling (2004) used a virtual reality paradigm and found that event-based PM was affected after stroke, but time-based PM was not. In contrast, Cheng, Tian, Hu, J. Wang, and K. Wang (2010) found that time-based, but not event-based PM, was impaired after thalamic stroke. Kim, Craik, Luo, and Ween (2009) performed a group study investigating PM performance in relation to different cognitive functions in 12 stroke patients. They observed that stroke patients have difficulties

in PM operations and speculate that these could be related to problems in self-initiated processing. The results from these studies do not fully clarify yet what cognitive mechanisms underlie PM deficits in stroke, and whether event- or time-based PM is mostly affected. The study by Kim et al. indicates that the type of processing needed to perform the task might be cardinal. There could be differences in task characteristics for both types of PM that determine performance.

In this regard, recent theories (e.g. Einstein et al, 2005) state that 'focality' seems crucial. Tasks where cue features are processed 'focally' (in that they overlap with information relevant to the ongoing task) should require few cognitive operations and resources. In contrast, non-'focal' PM tasks involve effortful self-initiated retrieval processing and strategic monitoring, as in time-based tasks where clock checking is a form of actively monitoring the appropriate moment of execution of an intended action. The extent to which different cognitive functions are addressed in PM task situations might depend on this distinction.

The current study aimed to systematically investigate the extent and nature of PM deficits in a considerably large group of stroke patients using a variety of event- and time-based PM tasks, and to link these to concurrent impairments in different cognitive domains.

Material and methods

Participants

In the University Medical Center Utrecht (UMCU) stroke patients are asked to participate in a longitudinal study on cognitive functioning after stroke, in accordance with inclusion regulations described in protocol 05-109 of the UMCU Medical Ethical Committee. For the current study we selected 39 patients. Inclusion criteria were diagnosis of stroke based on clinical assessment and imaging (CT, MRI), ability to travel independently, living at home, and willingness to participate. Exclusion criteria were diagnosed dementia, significant current psychiatric disorders (such as major depressive disorder), insufficient communicative ability (severe aphasia or non-fluent Dutch speakers), and other impairments that would limit participation or completion of the assessment (such as blindness).

Ischaemic strokes predominated (31% haemorrhagic). Average interval between date of stroke and testing was 17 months (SD = 8.3). No influence of elapsed time between event and test date was found on any variable. Location of lesion was confirmed by

an experienced neurologist (CJMF), using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans that were obtained according to clinical practice. For 15 patients only CT scans were available. All available scans were used to determine the ultimate structural damage as exactly as possible, using a human brain atlas as reference (Duvernoy, 1999). Time between the index event and most recent scan varied, with a median of 5 days (range 0-741). Lesion locations in patients were widespread throughout the brain; 18 patients had strokes in the right hemisphere, 13 in the left, and 8 showed bilateral damage. Two patients had a history of a previous stroke.

Fifty-three age- and education-matched control participants, without self-reported neurological or psychiatric disorders, were included. The control participants were either spouses or family of patients or volunteers who came to our attention through word of mouth. Written informed consent for patients and control participants was obtained. Participants were compensated for their time and travel expenses and treated in accordance with the Declaration of Helsinki.

Table 1 shows the characteristics of the patients and the control group. Control participants did not differ from the patients with respect to level of education (coded according to Verhage (1983), range 1 through 7 from less than primary school to university degree), (premorbid) intelligence (estimated using the Dutch version of the National Adult Reading Test, scores corrected for age and gender (Schmand, Lindeboom & Harskamp, 1992)), dexterity, and age, but were more often female than the stroke patients. Stroke is more prevalent in males (Wilson, 2013), and control participants typically included spouses and family members from the opposite sex. Potential influence of gender was therefore examined in all primary analyses.

Table 1 Patient and Control Participant Demographics

Variable	**Patients** ***N* = 39**	**Control participants** ***N* = 53**	***p***
Gender (% male)	69%	38%	.003*
Dexterity (right/left/ambidextrous)	89 / 8 / 3 %	89 / 9 / 2 %	.649
Educational level (median, IQR)	5 (5-6)	6 (5-6)	.156
Age *(M ± SD)*	58.2 ± 14.2	51.7 ± 17.4	.062
IQ *(M ± SD)*	107.8 ± 18.0	107.9 ± 12.9	.990

Note. Group differences between patients and control participants were tested using chi-square tests (gender, dexterity), Mann-Whitney U (educational level) and two-tailed independent t-tests (age, IQ). *$p < .05$

Tasks

An experimental prospective memory paradigm was developed, in which event-based and time-based assignments were integrated in a continuous performance task, the Bourdon-Wiersma task (Lezak, 1995). See appendix A for a detailed description of the PM tasks. Briefly, the Bourdon-Wiersma task entails marking arrays of four dots among arrays of 3-5 dots in varying configurations on a sheet of paper (see figure A.1). Two PM instructions were added to the standard instructions of the task. Participants were asked to call out the Dutch word for line ("regel") whenever the last configuration in a line contained 3 dots (event-based PM), and to insert a coin in a designated container after each minute passed (time-based PM). Participants were given the assistance of an external aid to monitor time.

As primary measures of event- and time-based PM, the percentages of correct responses on both tasks were calculated. The number of times participants used the timing aid was used as measure of monitoring behaviour. Ongoing task performance was measured by counting the number of lines finished within the task duration of ten minutes. An error score was calculated by the number of errors on the continuous performance task (false alarms and misses of crossing the configurations of 4 dots) per line.

In addition to the experimental task, two naturalistic PM tasks were administered that were designed to resemble every-day functioning. Participants were asked to remind the experiment leader to return their watch after finishing the last task (event-based), and to make a phone call after half an hour (time-based).

Scores were based on the accuracy of the performance of the time-based task (within a range of 5 minutes around the appropriate time a maximum score of 3 was given), and the amount of additional cues that were given before the task was executed (score 3 for correct performance without any (additional) cues, 2 or 1 depending on how many additional cues were needed and 0 for no recollection of the intention when asked). An example of a cue was the experimenter asking after 40 minutes "how much time do you think has passed since the first task?" (see Appendix A for a description of all cues).

Cognitive functioning was assessed by using standard neuropsychological tasks in the domains of retrospective memory, speed of processing and attention/executive functioning.

To measure retrospective memory, the Dutch version of the Rey Auditory Verbal Learning Test (Saan & Deelman, 1986) was administered. Three variables were used: immediate recall total score, delayed recall and recognition score.

Time scores of both conditions of the Trail Making Test (TMT (Corrigan & Hinkeldey, 1987)) were used as measures of speed of processing.

Attention/executive functioning was operationalised using measures of mental flexibility (index score of the TMT) and indices of working memory: the total score of the Letter Number Sequencing task (a subtest of the Wechsler Adult Intelligence Scale III (Wechsler, 1997) and product scores of the Corsi Block Tapping task forward and backward (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000).

Performances on the neuropsychological tasks were combined into normalized composite scores for the three cognitive domains, by calculating the mean Z-score and pooled SD for tasks in each domain.

Statistical analysis

Stroke-related PM performance was assessed in two ways. First, overall group comparisons were made for the various PM and other cognitive tasks. Univariate analyses of variances were used with group (patients versus control participants) and gender as fixed factors. Age was included as covariate. Bonferroni correction for multiple comparisons was applied.

Second, as the stroke population was heterogeneous in lesion location and therefore the patterns of cognitive failure could differ greatly between patients, case study methodology (Crawford & Howell, 1998; Crawford & Garthwaite, 2002; Crawford, Garthwaite, Azzalini, Howell & Laws, 2006) was used to detect deficits on individual level. Test scores for each patient were compared with control group statistics using two-sided modified independent t-tests, Bonferroni-corrected for multiple comparisons. As gender was differentially distributed over patient and control participant groups, separate control groups were composed for males and females. A significantly lower performance of an individual patient compared to the gender-matched control group on one of the tests in a given cognitive domain was considered to reflect a deficit in that domain. Differences in prevalence of PM deficits compared to those in retrospective memory, attention/executive functioning and processing speed were tested using Pearson chi-square tests of distribution of frequencies.

To investigate the communality between different measures of PM, Pearson correlations between naturalistic and experimental event- and time-based PM were computed in the total sample. The influence of monitoring behaviour on time-based prospective memory performance was also tested by Pearson correlation analysis.

To investigate the contribution of different cognitive functions on event versus time-based PM performances on the experimental task, linear regression analyses were performed on the total sample, entering normalized composite scores on each domain to the model as independents and subsequently group, age, gender and estimated IQ.

An explorative analysis of the relation with lesion location was performed to investigate whether specific brain regions were more often affected in patients that were selectively impaired in PM, compared with patients who did not show deficits in PM or other domains, and patients with deficits in other domains but not in PM.

Results

Overall group differences

Patients performed worse than control participants on different cognitive variables in the domains of retrospective memory, speed of processing and attention/executive functioning (see table 2).

Table 2 Group Differences between Patients and Control Participants

	Control participants		**Patients**		
Variable	***M* ± *SD***	***N***	***M* ± *SD***	***N***	***p***
RAVLT immediate recall	51.9 ± 11.6	53	40.0 ± 14.1	39	.001*
RAVLT delayed recall	11.3 ± 3.40	53	8.46 ± 4.12	39	.013
RAVLT delayed recognition	29.5 ± 1.23	53	27.2 ± 3.86	39	.004
TMT A time	31.1 ± 14.1	52	47.5 ± 23.1	39	.002*
TMT B time	64.5 ± 29.3	52	117.9 ± 92.2	39	.002*
TMT index	2.21 ± 0.94	52	2.49 ± 1.16	39	.382
Letter Number Sequencing	11.6 ± 3.02	53	8.62 ± 3.57	37	.001*
Corsi forward product score	48.9 ± 18.4	53	40.2 ± 12.8	38	.025
Corsi backward product score	56.5 ± 21.2	53	40.4 ± 18.3	38	.001*
TBPM nat	2.74 ± 0.45	53	2.59 ± 0.82	39	.452
EBPM nat	2.54 ± 0.75	52	2.44 ± 0.82	39	.879
TBPM exp	73.9 ± 24.4	52	48.5 ± 32.9	36	.002*
EBPM exp	95.9 ± 4.86	52	88.6 ± 19.9	36	.075
PM exp ongoing task performance	39.1 ± 7.30	52	31.7 ± 8.11	36	.001*
PM exp error score	0.65 ± 0.55	52	1.04 ± 0.81	36	.052
PM exp monitoring	20.0 ± 7.28	52	14.3 ± 5.73	36	.007

Note. Differences were tested using univariate analyses of variances, controlling for age and gender. RAVLT: Dutch version of the Rey Auditory Verbal Learning Test; TMT: Trail Making Test; TBPM: time-based Prospective Memory; nat: naturalistic; EBPM: event-based Prospective Memory; exp: experimental; PM: Prospective Memory.
*$p < .003$, corrected for multiple comparisons

In the PM tasks, significant group differences were found on the time-based condition of the experimental PM task and on ongoing task performance. No differences were found for the naturalistic measures of PM, possibly due to limited range of the scores, nor for the experimental measure of event-based PM, where most scores were close to ceiling.

No effects for gender and no significant interactions between group and gender were found.

PM deficits

Using the criterion of performance on one of the tests in a given domain significantly below the gender-matched control group mean on a modified independent samples t-test (as described in Crawford & Howell, 1998 and Crawford & Garthwaite, 2002), Bonferroni corrected for multiple comparisons, PM failure occurred in 16 patients (41%). This frequency is significantly higher than the prevalence of deficits in processing speed (23%, $\chi^2(1, N = 39) = 6.5$, $p = .011$) and attention/executive functioning (15%, $\chi^2(1, N = 39) = 5.2$, $p = .022$), but not significantly different from the frequency of deficits in retrospective memory (33%, $\chi^2(1, N = 39) = 3.4$, $p = .066$).

Of the 16 patients with PM deficits, 6 had only time-based PM deficits, 9 only event-based PM failure and 1 had failure in both.

PM deficits concurred with failure in other cognitive domains in 11 patients, but 5 patients showed failure in PM only.

Correlations between PM measures

To investigate the communality between different measures of PM, between-task correlations were examined in the total sample (see table 3). Experimental time-based PM significantly correlated with experimental event-based PM and time- and event-based naturalistic PM. These correlations are modest in size, and no significant correlations were found between the other variables. This shows that different types of PM overlap partly, and that there are considerable unique aspects of each PM variable.

Table 3 Correlations Between and Within Prospective Memory Variables for the Total Sample (N =92)

	Naturalistic TBPM	Experimental EBPM	Experimental TBPM
Naturalistic EBPM	.098	-.001	.261*
Naturalistic TBPM		.106	.244*
Experimental EBPM			.323*

Note. EBPM: Event-based prospective memory; TBPM: Time-based prospective memory. *$p < .05$, **$p < .001$.

Monitoring

Monitoring behaviour was positively correlated with time-based PM, r = 0.64, n = 92, $p < .001$. Participants who checked the time more often during the task, performed better at time-based PM. The size of this correlation is large.

Cognitive correlates of PM

Composite scores on each domain (Retrospective Memory, Attention/Executive Functioning and Speed of Processing) were entered as regressors, with experimental time- and event-based PM scores as dependent variables. Also, group, age, gender and estimated IQ were introduced in the regression models.

In figure 1, the different contributors to the models of EBPM and TBPM are visualized.

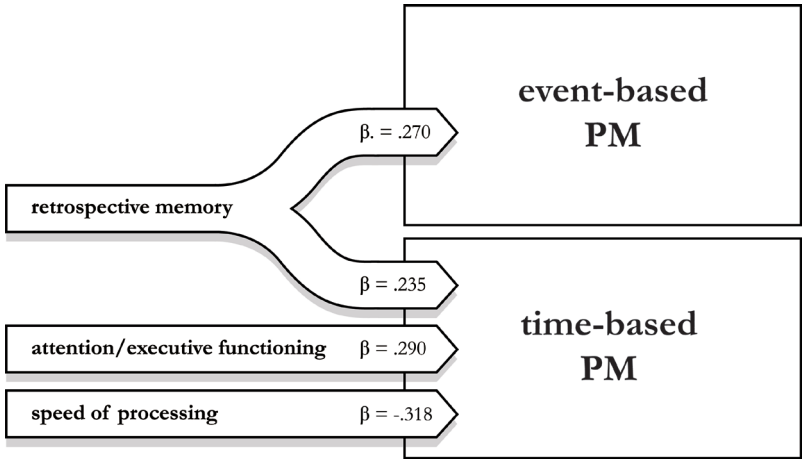

Figure 1. *Contributions of cognitive domains to event-based versus time-based prospective memory*

Retrospective Memory (β = .235, $t(81) = 2.44$, $p = .017$), Attention/Executive Functioning (β = .290, $t(81) = 2.88$, $p = .005$), and Speed of Processing (β = -.318, $t(81) = -2.95$, $p =$

.004) significantly predicted experimental time-based PM scores. This model explained a significant proportion of variance in experimental time-based PM, $R^2 = .496$, $F(3,81) = 26.56$, $p < .001$. Group, age, gender and estimated IQ did not significantly contribute to the regression model.

Retrospective Memory was also a significant predictor of experimental event-based PM (β. = .270, $t(83) = 2.56$, $p = .012$). Retrospective Memory explained a statistically significant, but small proportion of variance in experimental event-based PM, $R^2 = .062$, $F(1,83) = 6.55$, $p = .012$ (see figure 1). Attention/Executive Functioning and Speed of Processing did not contribute significantly when introduced to the regression model, neither did group, age, gender and estimated IQ.

Anatomical correlates

An explorative examination of the lesion localization in the group of patients with selective PM failure (n = 5) was performed. For lesion locations that were shared (i.e. were present more than once), we tested whether a lesion in that location was more prevalent in this group, compared with patients without failure in any of the tested domains (n = 17), or with failure in domains other than PM (n = 6).

For lesions in the precentral gyrus, postcentral gyrus, insula, caudate nucleus, putamen, corona radiata and internal capsule, no significant between-group differences were found ($p > .05$).

A difference in distribution was found for lesions in the superior temporal lobe (χ^2 (1, $N = 28$) = 10.514, $p = .005$), see figure 2. Lesions in the superior temporal gyrus (STG) were more prevalent in patients with selective PM failure compared with patients without PM failure. These STG lesions were all located in the right cerebral hemisphere (see figure 3).

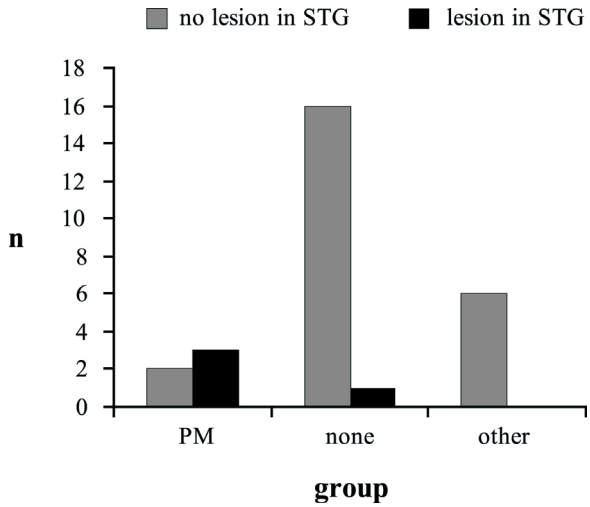

Figure 2. *Distribution of lesions in the superior temporal gyrus by group. Groups represent patients with selective prospective memory failure (PM), patients without failure in any of the tested domains (none), and patients with failure only in other domains (other).*

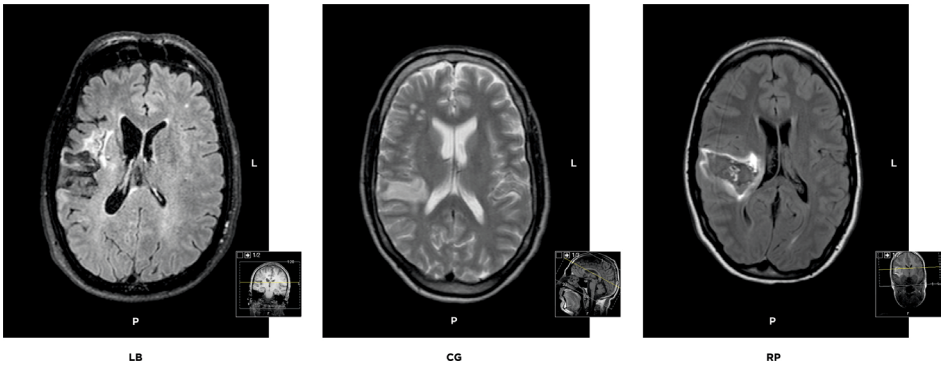

Figure 3. *Lesions including the right superior temporal gyrus in patients LB, CG and RP, who all show selective prospective memory failure. Transversal slices of T2 (CG) or T2-FLAIR (LB and RP) MR imaging are shown. In LB and CG a cortical infarction in the medial cerebral artery territory is visible. The MRI-scan of RP shows a lobar hematoma in the temporal lobe with extension towards the frontoparietal area.L = left hemisphere, P = posterior.*

Visual inspection showed that patients with STG lesions and selective PM deficits all had (superficial) mixed cortical and subcortical infarcts in the terminal branches of the middle cerebral artery, without signs of lacunar infarctions or white matter abnormalities indicative of small vessel disease. There were no differences in type of stroke (ischaemic or haemorrhagic) and imaging procedures (MRI or CT, scan protocols) between

these patients compared to the other patients in the sample. Nor were demographical characteristics different (age, gender, educational level, estimated IQ, dexterity)."

Discussion

In the present study we investigated cognitive correlates of prospective memory functioning in a stroke population. PM was found to be impaired in 41% of the patients with stroke. Deficits in PM occurred as frequently as impairments in retrospective memory (33%) and more often than impairments in attention/executive functioning (15%) and speed of processing (23%). In an extensive review (Snaphaan & de Leeuw, 2007), the prevalence of (retrospective) memory deficits ≥6 months post-stroke was estimated to vary between 11-49%. The proportion of PM deficits observed in the present study is relatively high compared with other estimates of cognitive function in this selected population of stroke patients. In addition, prospective and retrospective memory (RM) deficits did not always coincide, indicating that RM and PM may to some extent overlap, but can also be selectively impaired. The high prevalence of PM impairment in the current study shows the vulnerability of PM, and the relevance of regarding PM as a cognitive construct.

Different subtypes of PM have been distinguished in the literature (Gonneaud et al., 2011). Our results confirm that event-based and time-based PM are functionally dissociable. Despite (modest) correlation between performance in EBPM and TBPM, most patients were selectively impaired in either EBPM or TBPM; in only one patient both were affected. These findings strongly suggest that different processing components are involved in either type of PM.

We found that speed of processing, attention/executive functioning and retrospective memory all contributed to TBPM, but only retrospective memory was significantly involved in EBPM. These results corroborate previous findings (Carlesimo & Costa, 2011; Groot, Wilson, Evans, & Watson, 2002; Otani et al., 1997; Salthouse, Berish, & Siedlecki, 2004) and suggest that TBPM is a more complex cognitive operation than EBPM. The role of monitoring behaviour may be a key variable in this distinction. To perform an action at a certain moment in time, one would need to monitor time appropriately. Correlational analyses indeed showed that participants who checked the clock more frequently, performed better at TBPM. Also, patients showed less active monitoring behaviour compared with control participants. Monitoring behaviour involves effortful processing, which logically involves multiple cognitive operations.

The pattern of results, indicative of differential involvement of cognitive processes underlying EBPM versus TBPM, fits the 'focality' theory (e.g. Einstein et al., 2005). The recall of an intention in 'focal' tasks is reflexive-associative in nature, as opposed to self-initiated retrieval processes that are required for non-'focal' PM tasks. If, for example, the ongoing task involves a lexical decision (word categorization) and the PM cue (a specific word) also involves processing lexical information, PM retrieval occurs spontaneously. For non-'focal' PM tasks, effortful processing and strategic monitoring are needed. TBPM is non-'focal', with clock checking as a form of actively monitoring the appropriate moment of execution of an intended action. Our operationalization of EBPM was 'focal' in nature: the PM cue as well as the ongoing task involved the same process (determining the number of dots in a configuration). Therefore, no additional active search for the target was needed and fewer cognitive operations were involved. The conceptualization of 'focality' logically explains what components contribute to functionally distinguishable types of PM. These findings are in congruence with the multi-process framework (Einstein & McDaniel, 1990; Rose et al., 2010), which states that different cognitive components underlie PM functioning. When either of the components is affected by neural damage, PM performance can be impaired. However, to correctly perform a PM task, not only do these separate components need to be intact to a certain degree, but also they need to be integrated well.

Interestingly, despite the observed correlation between PM and other cognitive domains, PM was selectively impaired in 13% of the patients, suggesting there could exist unique properties of PM as well. In the patients with selective PM damage, lesions in the (right) superior temporal gyrus (STG) were present more often compared to patients with failure in other cognitive domains. We speculate that the STG, being a region that is associated with cross-modal integration (Ghio & Tettamanti, 2010; Robins, Hunyadi, & Schultz, 2009), could be crucial to integrate the different components needed for succesfull PM functioning. As a note of caution regarding this speculation, it should be mentioned that the methods used to explore anatomical correlates in this study were rather coarse, as the brain scans were collected within clinical care as usual (not standardized across the sample) and did not form a primary target of investigation. Interestingly, in a recent study by Gonneaud et. al. (2013), the left STG was found to be deactivated during a TBPM task. Follow-up research is needed to further investigate the involvement of the STG in PM.

The present study is one of the first to systematically examine functional correlates of PM performance in a group of patients with both haemorrhagic and ischaemic stroke. Strengths of the study include the detailed examination of different types of PM in both experimental and naturalistic tasks. Also, the patient sample was heterogeneous

in terms of lesion location, and therefore unpolluted by a priori selection bias of brain structures that were previously associated with PM. Follow-up scans were not available for all patients, therefore no firm conclusions can be made on size and severity of the strokes. The included sample consisted of community-dwelling stroke survivors. Particularly this independent group of patients, who still suffer from PM deficits in the long term, may need to rely on their PM most.

From a clinical perspective it should be mentioned that the present PM tasks are suitable for administration in standard neuropsychological assessment, and can offer valuable information on PM performance. The tasks that were used proved to be sensitive and detected failure even without failure on any of the other tasks, and as such provide additional diagnostic value. A limitation of the present study is that the used naturalistic tasks provide a relatively coarse indication of PM performance. The experimental tasks seem more suitable to distinguish between PM failure and intact functioning than the clinically most frequently used single-trial tests with dichotomous scores. Scores on the event-based task however did tend towards the maximum often, therefore some adjustments should be made to prevent ceiling effects.

Another limitation of this study might be that the control group as a whole tended to be younger than the patient group. Increasing age has been associated with PM deficits (see for reviews and meta-analyses Henry et al., 2004, McDaniel & Einstein, 2011, and Uttl, 2008). It should be noted, however, that age did not differ significantly between the two groups at the .05 significance level. Moreover, we also controlled for age in the main analyses by entering age in the regression models.

The finding that patients show less active monitoring behaviour, whereas in general increased monitoring is related to better non-'focal' PM performance, could stimulate development of new rehabilitation programs, in which patients learn to adapt strategies to compensate for PM deficits. Rehabilitation programs developed for PM so far are mainly focused on better encoding of the intention (Grilli & McFarland, 2011; McFarland & Glisky, 2012). Methods to improve monitoring of the intention may add additional value to these strategies.

In sum, the importance of PM as a construct that is sensitive to acquired brain damage is confirmed by this study. A multitude of different cognitive operations is involved in PM functioning. 'Focal' event-based PM is a relatively automatic process which involves retrospective memory. Time-based (non-'focal') PM is more complex as it calls for active monitoring and self-initiated retrieval. It is supported by speed of processing, attention/executive functioning and retrospective memory. Failures in PM as such are often

accompanied by other cognitive defects. However, in 13% of the patients a selective PM problem occurred. An explorative lesion analysis suggested that in particular the right STG might play a unique role in PM, possibly functioning as an integration hub.

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Appendix A:

Prospective Memory Tasks

Experimental PM

The Bourdon-Wiersma test (Lezak, 1995) was adapted as an ongoing task for a new method to investigate PM. This is a widely used vigilance task that involves sustained attention under time pressure. The task contains a sheet of paper composed of 50 horizontal lines containing 25 dot arrays, with each 3-5 black dots in varying configurations (see figure A.1). Two PM tasks (one event-based, one time-based) were added to the original instruction. Participants were thus required to perform three tasks in total. First, they were to mark each array of four dots on the testing sheet as quickly as possible, as in the original instruction. Participants were not allowed to correct themselves if they noticed any errors. Second, for the event-based task, at the end of each completed line, participants were to call out the Dutch word for line ("regel") whenever the last configuration in a line contained 3 dots.

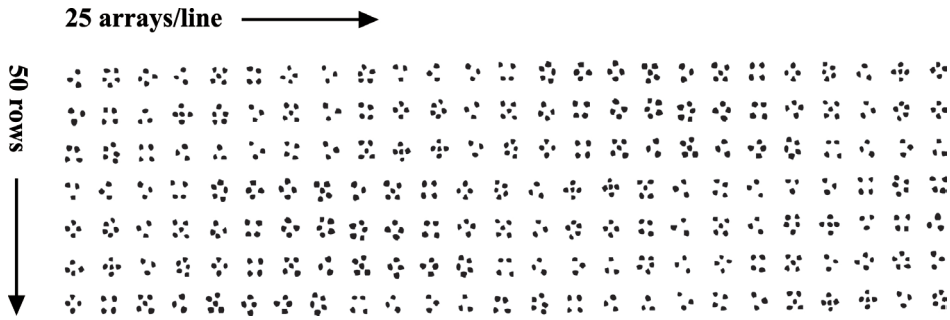

Figure A.1 *Stimulus material of the Bourdon-Wiersma Test (Copyright C. Weis, Groningen, The Netherlands, 1998)*

Third, a time-based PM task had to be performed. Participants had to insert a coin into a designated container at the beginning of every new minute since the start of the experiment. This required participants to perform an action unrelated to the ongoing task. Coins came from a stash of 20+ identical coins. Participants were given the assistance of an external aid to keep track of time, in line with previous research (e.g. Einstein, McDaniel, Richardson, Guynn, & Cunfer, 1995; Groot, et al., 2002; Hicks, Marsh, & Cook, 2005; Shum, Valentine, & Cutmore, 1999). Participants could summon a digital timer with the press of a button. The elapsed time since the beginning of the task would be visible for three seconds (in a Min: Sec format), and the response was logged. Participants were instructed to check the time as often as they wanted. Participants received verbal and written instruction about the procedure and could not start until

they were able to repeat the three tasks verbally. Participants were unaware of the total time that the task would last. After ten minutes, task execution was terminated. If a participant was able to finish all 50 lines before this time, the experiment was terminated when he/she finished the last line.

Various performance scores were obtained in this task. Ongoing task performance was measured by counting the number of lines finished during the task, and calculating the number of errors (false alarms and misses of crossing the configurations of 4 dots) per line.

As a measure of event-based PM, the proportion of correct responses (say 'regel') for the lines that ended with a 3 dot configuration was calculated.

A measure of time-based PM was obtained by calculating the proportion of coins inserted at the correct time (within the range of 5 seconds around each full minute) for the duration of the task. The number of times participants used the timing aid was used as measure of monitoring behaviour.

Naturalistic Prospective Memory

A modified version of the personal belonging task (B. Wilson, Cockburn, Baddeley, & Hiorns, 1989) was used to assess PM performance in a naturalistic manner, as an ecologically valid indication of daily life functioning. For the event-based task, at the beginning of the experimental test session, a personal belonging was requested. If the participant was wearing a watch then this item was taken; otherwise a cell phone, house keys or something of similar value. The personal belonging was placed in a drawer and participants were instructed to ask for its return upon being told later in the testing session: "we are now finished with all of the tests". Those participants who requested the return of their belonging at the appropriate moment were awarded a maximum score of 3. If they did not respond, cues were given by the experimenter: participants obtained score 2 if they requested their item back after the experimenter walked up to the drawer, and score 1 if they did so after the experimenter asked next whether there was anything still do be done. If still no response was given, a score of 0 was received.

For the time-based task, participants were told to remind the experiment leader to make an important phone call after half an hour. The phone number was written on a 'sticky note', which was placed on the right hand upper side of the desk, and thus remained in (peripheral) sight during the test session. Participants received the maximum score of 3 if they gave the reminder when half an hour had passed (or within a range of 5 minutes around the exact time). When the reminder was given within a range of 10 minutes

around the exact time, or after the first cue (experiment leader asking after 40 minutes "how much time do you think has passed since the first task?") a score of 2 was given. Score 1 was awarded for correct response after the second cue (asking what the note was for). When no response was given after the second cue, a score of 0 was received.

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4

Prospects for Prospective Memory: Analyses of Cognitive Models for Prospective Memory

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Abstract

Prospective Memory (PM) is remembering what to do at a specific point (occasion) in the future. Over the past decades the number of publications on the topic has risen, as has debate about the concept.

Contemporary data-driven theories on the cognitive components that underlie PM have been proposed, differing in specific claims. In the present study, confirmatory statistical methods were applied to directly compare differential hypotheses with regard to the role of sequential processing, visuospatial processes and ongoing task performance trade-off effects on event-based (EB)PM and time-based (TB)PM. No support was found for any of the hypotheses that were formulated in a theory-driven fashion. However, indications for functional dissociations between different types of PM were found when explored in a data-driven manner. Verbal working memory, time perception and monitoring were associated with TBPM, and ongoing task behaviour predicted EBPM performance.

This attempt to find confirmation of different ideas on PM did not lead to firm answers. We conclude that to bring PM research further, the next step should be to further systematically evaluate existing theories on PM, to build a firmer base under the theoretical framework of PM.

Introduction

Prospective Memory (PM) is remembering what to do at a later point in time, such as arriving on schedule for your appointment at the hair salon (time-based: TBPM), or when a certain event occurs, for example remembering to bring your keys as you leave the house (event-based: EBPM). In the past decades the number of articles published in this field has risen exponentially (Carlesimo & Costa, 2011), and it has gained recognition as a relevant topic (Costa, Carlesimo, & Caltagirone, 2012). However, as the body of research grows, debate about the concept evolves as well. One question that has been posed is why participants often perform worse on time-based tasks than on event-based counterparts when instructions of comparable complexity are used. Groot, Wilson, Evans, and Watson (2002) explain such findings by postulating that this difference in difficulty is due to the fact that time-based tasks require greater inhibitory control, and place higher demands on retrospective memory and executive functions. Based on similar results, Shum, Valentine, and Cutmore (1999) argue that this difference in performance might be due to the fact that time-based tasks do not use external cues and need more self-initiation. A recent study from our group (Kant et al., 2014) showed EBPM to be a relatively simple and automatic process that is supported by retrospective memory. TBPM proved to be more complex, requiring active monitoring of the environment. TBPM performance could be predicted by processing speed, attention/executive functioning and retrospective memory.

The previous findings suggest that multiple cognitive components are important in PM, and to a different degree for event- and time-based variants. In line with this suggestion, several data-driven theories and hypotheses have been proposed about the cognitive architecture underlying PM ((Harris & Wilkins, 1982; Kalzoupos, Eriksson, Sjölie, Molin, & Nyberg, 2010; McDaniel and Einstein, 2011; Rose, Rendell, McDaniel, Aberle & Kliegel, 2010). McDaniel and Einstein (2000, 2011) have proposed a multi-process theory of PM in which both strategic, attention-demanding processes as well as relatively automatic mechanisms are important. Which of the two is most dominant depends on the specific situation in which PM is initiated. One of the crucial determining factors within this multi-process framework is thought to be *´focality'*: the level of overlap between the cue and the ongoing task. When a cue is presented in a way that it is processed within the context of the ongoing task, prospective remembering should occur automatically. When the cue is unrelated to the ongoing task, active monitoring of the environment would be necessary, which requires more resources (McDaniel & Einstein, 2007).

In the present study a confirmatory approach was applied to verify ideas that have emerged about the architecture of PM, focusing on the cognitive components underly-

ing event- and time-based PM. The aim was to directly compare different assumptions that followed from previous exploratory research (see below), using a Bayesian model selection approach developed to evaluate informative hypotheses (Mulder, Hoijtink, & de Leeuw, 2012). Informative hypotheses are hypotheses representing specific a priori expectations of outcomes by imposing equalities and inequalities (larger and smaller than restrictions) on the model parameters. Through this Bayesian approach differential support can be found for each of the models, indicating which of these models describes the data best.

The differential involvement of cognitive processes (the independent factors) in EBPM versus TBPM (the dependent factors) was analyzed by multivariate multiple regression. Investigating how different cognitive processes contribute to each type of PM could validate current theoretical models and thus improve our understanding of mechanisms underlying PM.

Experimental data were acquired through an extensive battery of cognitive tests that together reflected the complex cognitive architecture underlying PM, as based on literature. PM was operationalized using a parallel dual-task paradigm, with EBPM and TBPM as primary outcome measures and monitoring behavior and ongoing task performance as possible influencing factors. This task has been shown to differentiate between cognitive components underlying EBPM versus TBPM in a sample of stroke patients (Kant et al., 2014). Various experimental tasks were included: those that tap processes which have previously been associated with PM (i.e. executive functioning, time perception) evidently inspired by leading theories on PM as well as tasks involving processes that arguably might connect to PM, but as yet to an unknown extent (e.g.visuospatial memory). Several theoretical models were considered in a layered approach, in which those variables were grouped together that could be linked to joint underlying theories.

First, we investigated whether the data reflect the idea that sequential processes are more involved in TBPM than in EPBM, based on the so-called Test-Wait-Test-Exit (TWTE) model for strategic monitoring (Harris & Wilkins, 1982). This model states that keeping track of time is necessary for adequate clock checking in TBPM paradigms. Estimating the passage of time as a key function in monitoring behavior in TBPM has been confirmed by other authors (e.g. Mäntylä, Carelli, & Forman, 2007; Glickson & Myslobodsky, 2006), but not by all (Williams, Boucher, Lind, & Jarrold, 2013; Zinke et al., 2013). Time perception has been related to verbal working memory (Baudouin, Vanneste, Isingrini, & Pouthas, 2006), as both involve sequential processing. One might expect that other sequential processes such as episodic temporal memory are also related to TBPM. There-

fore, verbal attention and working memory as well as temporal order memory were also included in this hypothesis. Sequential processes such as monitoring the passage of time should not be necessary for EBPM performance, as it asks for execution of an intention coupled to an external cue instead of a moment in time. Therefore, sequential processes were expected to be stronger related to TBPM than to EBPM. This hypothesis was tested against the idea that no differences would be found in the influence of the abovementioned variables on the dependent variables (TBPM and EPBM), which can be regarded as a null-hypothesis.

The second model states that visuospatial processes are more involved in EBPM than in TBPM. To our knowledge, no previous research has specifically focused on this distinction; therefore this hypothesis is more speculative in nature. There is some evidence that spatial attention and episodic working memory are related to EBPM. Kalzoupos et al. (2010) performed an fMRI study and showed parietal brain regions to be activated during intention maintenance and between target detection and action in a virtual reality EBPM paradigm. This activation is thought to reflect top-down and bottom-up attentional processes that direct attention to the cue and match the external environment with the internal representation of the intention in memory. Visuospatial attention and spatial episodic working memory processes can therefore be expected to be involved in EBPM, especially in paradigms where the EBPM cue is related to a spatial position. TBPM does not require scanning of the environment, as no external cue is present and it merely involves self-initiated retrieval. Therefore, it was hypothesized that visuospatial processes would be involved to a greater extent in EBPM than in TBPM. This idea was tested against the hypothesis that there are no differences in the involvement of visuospatial processes on EBPM versus TBPM.

The third model regards the role of ongoing task performance. The first alternative hypothesis here states that ongoing task performance is positively related to EBPM performance as it may reflect higher vigilance. Detection of target events is thought to improve with higher vigilance (Foldi, White, & Schaefer, 2005; Baddeley, Cocchini, Della Sala, Logie, & Spinnler, 1999). Higher overall vigilance thus could facilitate detection of the EBPM cue, leading to activation of the memory trace of the intention. Because there is no external cue in TBPM, no relation was expected between ongoing task performance and TBPM, and therefore no or a smaller effect should be found on TBPM. The second alternative hypothesis states that ongoing task performance is negatively related to TBPM performance. There could be a trade-off between ongoing task performance and PM performance because TBPM performance requires effortful processing (Rose et al., 2010). Therefore, it was expected that the more resources are allocated to the TBPM task, the fewer reserves are left for the ongoing task. Ongoing

task performance would then not have any effect on EBPM task performance, as our EBPM task is *focal*, which involves automatic processing. These alternatives were tested against the hypothesis that there would be no difference in the influence of ongoing task performance on TBPM versus EBPM.

Methods

Participants

102 participants (37% male, age 18-31 (mean = 21.9, SD = 2.8)) were recruited with on-campus advertisements on bulletin boards at the University of Utrecht. Age did not significantly differ between males and females. None of the participants (had) suffered from any neurological or psychological disorder, nor reported to be colorblind. Written informed consent was obtained and each participant was either paid 12 euros or received course credits for participation. Participants were treated in accordance with the Declaration of Helsinki, and as described in protocol 05–109 of the UMCU Medical Ethical Committee.

Measures

Prospective Memory

To assess PM, a dual-task paradigm was used with event- and time-based PM tasks integrated in a continuous performance task, as described in Kant et al. (2014). The ongoing task involved marking configurations consisting of 4 dots as fast as possible, on a standardized testing sheet composed of 50 horizontal lines, each containing 25 configurations of 3-5 black dots in varying configurations, adapted from the Bourdon-Wiersma test (Lezak, 1995), see figure 1.

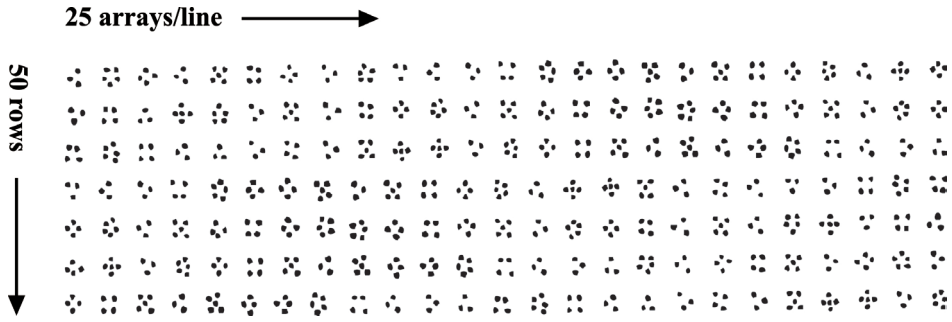

Figure 1. *Stimulus material of the Bourdon-Wiersma Test (Copyright C. Weis, Groningen, The Netherlands, 1998), used as Prospective Memory task*

For the event-based task, at the end of each completed line, participants were to call out the Dutch word for line ("Regel") whenever the last configuration in a line did not contain 4 dots (i.e., whenever it contained 3 or 5 dots).

A time-based task was to be executed at the start of each passing minute. Every minute into the experiment, participants were to insert a coin into a designated container. These coins came from a stash of 25 identical (5-eurocent) coins lying within vision and reach of the participant. Participants were given the assistance of an external aid to keep track of time, in line with research by e.g. Hicks, Marsh and Cook, 2005; Groot et al., 2002; Shum et al., 1999 and Einstein, McDaniel, Richardson, Guynn and Cunfer, 1995. A digital timer was programmed with E-prime™ software (PST Tools®), which showed the elapsed time since the beginning of the Bourdon Wiersma Task in a Min: Sec format. Participants could summon the clock on the screen with the press of a button. The timer would be visible for three seconds. Participants could check the time as often as they wanted. After ten minutes, task execution was terminated. If a participant was able to finish all 50 lines before this time, the experiment was terminated after the last finished line (which was the case for 21% of the participants).

Various performance scores were obtained in this task. A measure of TBPM accuracy was obtained by calculating the percentage of coins inserted at the correct time (i.e. within a 5 second range around each full minute). A measure of EBPM was obtained by calculating the percentage of appropriate "Regel" signals participants had given. Ongoing task performance was calculated by counting the total number of correctly processed configurations: 25 times the number of lines finished, minus the total amount of errors (false alarms and misses) on the ongoing task. A measure of monitoring behavior was obtained by counting the number of times participants used the timing aid.

Visuospatial Attention and Working Memory

The Corsi-Block task (Kessels, van Zandvoort, Postma, Kappelle, & de Haan, 2000) was used as a measure of visuospatial attention and working memory. The task uses an asymmetrical array of unmarked blocks, which the experimenter taps in sequence at a rate of approximately 1 block per second. Participants try to reproduce each sequence by tapping the correct blocks in the correct order in response. Participants were given both forward and backward variations of the task. All sequences, and the array of blocks, were derived from Kessels et al. (2000).

The length of the longest sequence that was successfully reproduced reflects the participants' maximum spatial working memory and attention span. This number multiplied with the total number of correctly reproduced sequences produced a Corsi Score.

This measure has been shown to be a reliable indicator of spatial working memory and attention and is sensitive to individual differences (Kessels et al., 2000). Forward and backward Corsi Scores were added to obtain one measure of spatial working memory and attention for each subject.

Verbal Attention and Working memory

The Digit Span Task (Baddeley, 1983; Baddeley & Della Sala, 1996) was used to assess verbal attention and working memory. Participants were to correctly repeat numerical sequences verbally presented to them by the experimenter. Sequence length was increased in regular intervals according to standard procedure. In the 'forward' condition, participants were to repeat each sequence of numbers in the same order (attentional span). In the 'backward' condition, participants were instructed to repeat the sequence in reversed order (working memory).

Participants' scores were calculated in a similar fashion as for the spatial working memory and attention measure. The maximum sequence length that could be repeated without error was multiplied with the total number of correct trials in each condition to produce a Digit Score for both the forward as well as the backward variation. These were added to obtain a single score for verbal attention and working memory for each subject.

Spatial and Temporal Episodic Working Memory

To test spatial and temporal episodic working memory, an experiment was designed using Object Relocation© software (Kessels, Postma, & de Haan, 1999). Experimental procedures and stimulus material were adapted from a study by Postma, Van Asselen, Keuper, Wester and Kessels (2006). Stimuli were colored images of highly familiar objects that were presented on a 17" touch-sensitive LCD monitor (ELO Accutouch®, resolution = 1024x768, viewing distance = 65 cm), on a gray background in a 19 x 19 cm square frame. Average stimulus size was 1 x 1 cm. Stimuli were never reused in the experiment. Participants selected and relocated the objects on the touch-screen. The task encompassed five different task conditions (see figure 2). Each condition contained one practice run and two experimental trials. Before the experimental procedure started, participants were familiarized with the task environment.

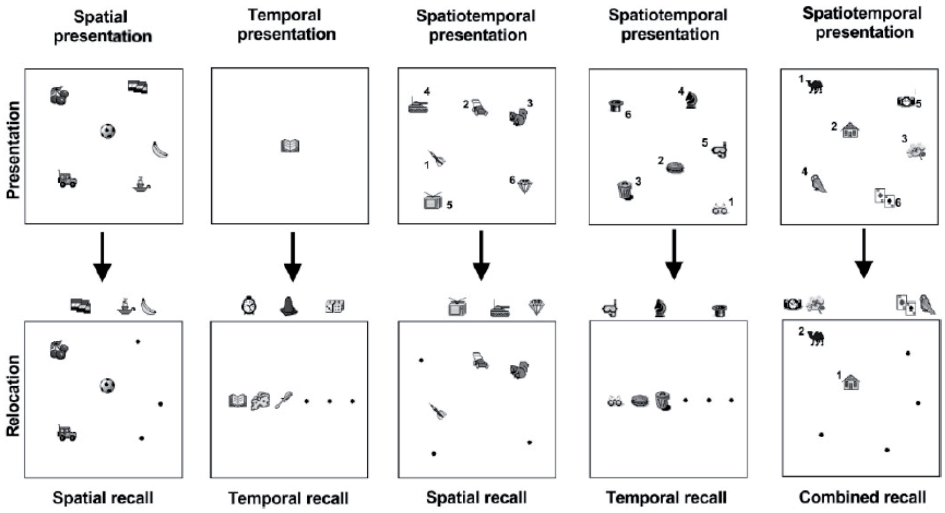

Figure 2. *Spatial and Temporal Episodic Working Memory taskconditions(adapted from Postma et al., 2006)*

In the first experimental condition, six objects were shown simultaneously for 18 seconds, at different locations distributed within the square frame. Next, these objects reappeared in random order above the square frame. Participants were instructed to relocate the objects to their correct positions, which were marked by black dots in the square frame. In the second condition, six objects were shown serially, each object for three seconds, always in the middle of the frame. Next, these objects were presented simultaneously in random order above a one-dimensional horizontal array of six dots. Participants were instructed to place the objects in the correct temporal order on the dots, i.e. the leftmost dot should be assigned the object that was presented first and the rightmost dot should be assigned the last shown item. In the third condition, six objects were shown serially for 3 seconds, each at a different location. Next, participants had to relocate the objects to their correct position. In the fourth condition, presentation was identical to the previous condition, but participants had to arrange the objects in their correct temporal order in a horizontal row of dots. In the fifth condition, presentation was similar to the previous two conditions. In the recall phase, objects were to be placed at their correct location in the correct temporal order. For each condition the percentage of incorrectly relocated objects was calculated. For the fifth condition, a percentage incorrect was obtained for spatial and temporal recall separately. A combined score for temporal episodic memory was calculated by averaging the percentages incorrect for all temporal measures (first condition, third condition and temporal score for the fifth condition), and a combined score for spatial episodic working memory was calculated by averaging the scores for all three spatial scores (second condition, fourth condition and spatial score for the fifth condition).

Time Perception and Comparison

For this task, three variants of time perception (time estimation, time production and time reproduction) were operationalized in the auditory modality using a dual-task paradigm. All variants were created with E-prime™ software (PST Tools®) and were administered on the computer. All auditory stimuli took the form of a three note C-E-G chord with C at a frequency of 261.63 Hz (C4). Durations in each task were 2, 5, 8, 12, 15 and 20 seconds, and each stimulus was administered twice, creating a total of 12 trials per task. These intervals were adapted from durations used in a study by Barkley, Edwards, Laneri, Fletcher and Metevia (2001) and chosen because they are all believed to fall within the time span of working memory (Baddeley, 1986, Mimura, Kinsbourne & O'Connor, 2000). Sound was played through a standard set of computer speakers at a fixed volume for all participants.

To minimize the effect of (sub-vocal) counting strategies, a secondary task had to be performed in parallel with each time perception task. During presentation of each stimulus, participants were instructed to pay attention to a colored rectangle (3.8 x 4.0 cm, or 138 x 143 pixels) at the center of the screen. At pseudo-random intervals, the color of this rectangle would change, at which point the subject was instructed to verbally report on the new color. There were four possible colors (red, blue, green and yellow) and six possible intervals (1500, 1700, 1900, 2100, 2300 and 2500 milliseconds). Participants were reminded that the accompanying time perception task should be given the highest priority. After a practice trial of 9 seconds for each condition, the experimental trials followed.

In the first condition (time estimation), participants were tasked to estimate the length in seconds of auditory stimuli ("tones") presented to them. Their response was recorded on a scoring sheet. A measure of performance was calculated by averaging the signed error in the verbal estimations, in seconds. In the second condition (time production), participants were asked to create tones with specified lengths. Participants were to press and hold a response box button for the specified length, while performing the secondary task. While holding the button, the C-chord was played through the speakers. A measure of performance was obtained by averaging the signed error in the intervals produced. Performance scores of the first and second condition were combined to obtain one measure of time perception. In the third condition (time reproduction), participants were tasked to replicate the duration of a "sample tone". After presentation of the stimulus, participants had to press and hold a response box button to replicate the "sample tone". Both during presentation of the sample tone and reproduction, the secondary task had to be performed in parallel. Performance scores were calculated

by averaging the signed reproduction error for all trials, creating a measure of time comparison.

Data Analysis

Statistical model and variables

The outcome of interest in the current study was not merely what predictor variables are linked to either dependent variable (event- and time-based PM) separately, but we were interested in functional dissociations between them, and therefore in the *relative* contribution of different cognitive processes to these two types of PM. Therefore, the differential involvement of the predictor variables on both outcome variables (see table 1 for an overview of the included variables) was investigated with the *multivariate* multiple regression model:

$$y1_i = \beta_{11}\, x_{1i} + \beta_{21}\, x_{2i} + \beta_{31}\, x_{3i} + \beta_{41}\, x_{4i} + \beta_{51}\, x_{5i} + \beta_{61}\, x_{6i} + \beta_{71}\, x_{7i} + \beta_{81}\, x_{8i} + \varepsilon_{1i}$$
$$y2_i = \beta_{12}\, x_{1i} + \beta_{22}\, x_{2i} + \beta_{32}\, x_{3i} + \beta_{42}\, x_{4i} + \beta_{52}\, x_{5i} + \beta_{62}\, x_{6i} + \beta_{72}\, x_{7i} + \beta_{82}\, x_{8i} + \varepsilon_{2i}$$

where β_{pk} (p=1,... ,8; k=1,2) denote the relations between predictor x_p and outcome y_k (variables are specified in table 1), and ε_{pi} are assumed to be bivariate normally distributed. Notably, no intercepts are included, as the regression coefficients are standardized.

Table 1 Variables

Dependent variables:	**Computation:**
y1. Time-based prospective memory	Percentage correct coin
y2. Event-based prospective memory	Percentage correct 'regel'
Predictor variables:	
x1. Visuospatial attention and working memory	Corsi product score forward+backward
x2. Verbal attention and working memory	Digit product score forward+backward
x3. Spatial episodic working memory	Object relocation spatial conditions % incorrect
x4. Temporal episodic working memory	Object relocation temporal conditions % incorrect
x5. Time perception	Time production & estimation mean error
x6. Time comparison	Time reproduction mean error
x7. Monitoring behavior	Number of time-checks
x8. Ongoing task performance	Bourdon-Wiersma errors and speed

Bayesian model selection

Following up on data-driven theories, a confirmative approach was applied using Bayesian model selection. With this approach, different competing alternative models could be directly tested against each other. This is more informative than comparing

each model against a null hypothesis according to the more traditional approach, as the hypotheses state what the researcher wants to know. The comparison between traditional hypothesis testing and Bayesian model selection is explained in methodological literature (e.g. Hoijtink & Klugkist, 2007; Klugkist, Van Wesel & Bullens, 2011; Kuiper & Hoijtink, 2010).

Inferences from data-driven theories were made on the contribution of different cognitive processes on EBPM and TBPM. These inferences were transformed into specific expectations about the relative size of the regression coefficients of each predictor variable for both dependent variables (EBPM and TBPM). These expectations were formulated in terms of constraints on the regression coefficients linking the predictors with the two outcome variables (TBPM and EBPM) by inequalities (larger and smaller than restrictions) and equalities between the model parameters. Each alternative hypothesis is a constrained version of the multivariate regression model. The relative support for these hypotheses was compared against the 'unconstrained' hypothesis (Hunc), which is the regression model without added constraints.

In the Bayesian model selection approach, the relative support for each informative hypothesis against the 'unconstrained' hypothesis is expressed by the Bayes factor (BF). When the BF is smaller than 1, it indicates that the hypothesis is not supported by the data. When the BF exceeds 1, it shows support for a hypothesis, and the larger the BF, the better the fit between the data and the constraints. In this fashion, one can also compare constrained hypotheses against each other; if the BF for one model is 5, and the BF for a second model is 20, then the support for the constraints of the second hypothesis can be said to be 4 times stronger than for the first.

The BF also takes into account the complexity of a hypothesis: it corrects for the amount of constraints in more specific hypotheses.

The Bayesian analyses were performed with the software BIEMS. An elaborate description of the methodology can be found in the accompanying manual by Mulder et al. (2012).

Note that an important issue in Bayesian analyses is the (subjective) specification of prior distributions. However, in the context of inequality-constrained models, Klugkist, Laudy and Hoijtink (2005, univariate normal model) and Mulder, Hoijtink & Klugkist (2010, multivariate normal models) showed that under some specification rules, the model selection is hardly affected by the prior specification and can therefore be

considered objective. The current analyses, performed with BIEMS, met these rules and therefore no prior distributions were specified.

Informative hypotheses

Hypothesis 1

H1a: sequential processes (verbal attention and working memory, temporal episodic working memory, time perception and monitoring) are involved in TBPM, to a greater extent than in EBPM. No constraints were included on the other predictor variables. This hypothesis is abbreviated as 'sequential TBPM>EBPM'.

H1b: there is no difference in the extent to which sequential processes are involved in TBPM versus EBPM. This hypothesis is abbreviated as 'sequential TBPM=EBPM'.

Hypothesis 2

H2a: Spatial processes (visuospatial attention and working memory and spatial episodic working memory) contribute to EBPM, to a greater extent than to TBPM. This hypothesis is abbreviated as 'spatial EBPM>TBPM'.

H2b: there is no difference between the extent to which visuospatial processes contribute to EBPM and TBPM. This hypothesis is abbreviated as 'spatial EBPM=TBPM'.

Hypothesis 3

H3a: ongoing task (OT) behavior influences EBPM: with higher vigilance (indicated by better ongoing task performance), the chance increases that the memory trace will be activated when processing the (*focal*) EBPM cue (due to a lower threshold for signal detection). Because the OT is unrelated to the TBPM task a smaller or no effect was expected on TBPM. This hypothesis is abbreviated as 'OT profit EBPM>TBPM'.

H3b: ongoing task behavior influences TBPM: there should be a tradeoff between OT performance and TBPM performance: the OT only suffers from the PM task or vice versa when it requires effortfull processing, as in our operationalization of TBPM. Our EBPM task is *focal* and thus should involve automatic processing. In this case, OT performance should not have any effect on EBPM performance. This hypothesis is abbreviated as 'OT trade off TBPM, not EBPM'.

H3c: there is no difference in the effect of OT performance on EBPM versus TBPM. This hypothesis is abbreviated as 'OT effect EBPM=TBPM'.

N.B. The direction of the inequality constraints depends on the scale of the performance scores. For example, when higher values reflect better performance and the (expected) relation is positive, the regression coefficient is greater than zero, but when higher values represent worse performance (as with time estimation error scores) it is smaller than zero (see table 2).

Table 2 Informative hypotheses

Hypothesis	(in)equality constraints
H1a	$\beta_{21}>(\beta_{22},0)$ and $\beta_{41}<(\beta_{42},0)$ and $\beta_{51}<(\beta_{52},0)$ and $\beta_{61}<(\beta_{62},0)$ and $\beta_{71}>(\beta_{72},0)$, β_{11}, β_{12}, β_{31}, β_{32}, β_{81}, β_{82}
H1b	$\beta_{21}=\beta_{22}$ and $\beta_{41}=\beta_{42}$ and $\beta_{51}=\beta_{52}$ and $\beta_{61}=\beta_{62}$ and $\beta_{71}=\beta_{72}$, β_{11}, β_{12}, β_{31}, β_{32}, β_{81}, β_{82}
H2a	constraints of H1 plus $\beta_{12}>(\beta_{11},0)$ and $\beta_{32}<(\beta_{31},0)$, β_{81}, β_{82}
H2b	constraints of H1 plus $\beta_{12}=\beta_{11}$ and $\beta_{32}=\beta_{31}$, β_{81}, β_{82}
H3a	constraints of H1/H2 plus $\beta_{82}>(\beta_{81},0)$
H3b	constraints of H1/H2 plus $\beta_{82}=0>\beta_{81}$
H3c	constraints of H1/H2 plus $\beta_{82}=\beta_{81}$

Note. βpk = regression coefficient of predictor variable xp on dependent variable yk. For example, $\beta_{21}>(\beta_{22},0)$ indicates the constraint that the regression coefficient of predictor variable 2 on dependent variable 1 is greater than the regression coefficient of predictor variable 2 on dependent variable 2, and also greater than zero. In successive hypotheses, the constraints of the former hypothesis that received the most support were included in subsequent hypotheses. Elements separated by commas represent sets with the same prediction. For example, in H1a, β_{21} was predicted to be larger than β_{22} and also larger than zero, without including a prediction about the relation between β_{22} and zero.

Additional null-hypothesis

After evaluating the competing hypotheses for each model, an additional null-hypothesis was added to check whether the proposed models explain the data better than the alternative hypothesis that none of the predictor variables contribute to PM. This model states that, for all included predictor variables, the regression coefficients equal zero for both EBPM and TBPM.

Additional exploratory analyses

Exploratory analyses were performed post hoc, to explore possible patterns in the data that were not included in the Bayesian hypotheses. These analyses were aimed primarily at finding suggestions for follow-up research, to generate hypotheses to be tested in a new sample, and not as confirmation of any theory (for argumentation supporting this approach, see Kuiper & Hoijtink, 2010).

To further examine the data, we performed several analyses. First, we performed binary logistic regression analyses to examine whether any of the individual predictors con-

tributed significantly to EBPM or TBPM performance, and which. To be able to perform this analysis, scores on the outcome variables were dichotomized by grouping the scores on the EBPM and TBPM task in optimal and suboptimal performance: maximal scores of 100% correct indicated optimal performance, scores below 100% indicated suboptimal performance.

Second, we explored the discriminative ability of the operationalization of EBPM and TBPM that was used, by observing dissociations in patterns of performance for different participants. When (double) dissociations would be found between participants who performed optimal on EBPM and suboptimal on TBPM or vice versa, this would indicate that the tasks that were used are able to discriminate between performances on either process.

Third, groups of participants were compared who performed optimal on EBPM and suboptimal on TBPM, vice versa, optimal on both and suboptimal on both. These four groups were compared on their performance on the individual predictors by multivariate analysis of variance (MANOVA), with task performance on each included variable as dependents. Differences in means between the first two groups would indicate differential involvement of cognitive processes in EBPM versus TBPM. Where the differences lie and in what direction would be explored and tested using post-hoc ANOVAs and t-tests.

Results

Overall performance

Descriptive statistics are shown in table 3. There was no issue of collinearity between the predictor variables. Correlations between these variables varied between .01 and .28, small to medium according to Cohen (1988).

Table 3 Descriptive statistics for the total sample (N=102)

Variable	Mean (SD)	Range	*r* y1	*r* y2
y1. Time-based PM	64.79(23.27)	9.09-100		-.01
y2. Event-based PM	94.38(6.22)	66.67-100		
x1. Spatial WM/attention	131.67(34.36)	64-208	-.12	.03
x2. Verbal WM/attention	108.84(35.28)	40-196	.27	.07
x3. Spatial episodic WM	7.66(9.08)	0-41.67	-.20	.20
x4. Temporal episodic WM	3.35(5.38)	0-20.83	-.01	.13
x5. Time perception	3.14(1.80)	1.00-9.18	-.11	-.05
x6. Time comparison	2.25(0.87)	0.57-5.64	.00	-.17
x7. Monitoring	19.72(8.63)	1-46	.42	-.07
x8. OT performance	1073.37(135.36)	668-1247	.18	-.11

Note. For y1, y2, x1, x2, x7 and x8 higher values represent better performance. x3, x4, x5 and x6 are error scores where higher values represent worse performance. PM = prospective memory task, WM = working memory, OT = ongoing task.

Bayesian model selection

All hypotheses that postulated differences in the influence of cognitive processes on TPBM versus EBPM received less support than hypotheses that stated equal contributions on either type of PM (see table 4).

Table 4 Bayes factors comparing each constrained with the unconstrained model

Hypothesis	Bayes factor
H1a: sequential TBPM > EBPM	10.77
H1b: sequential TBPM = EBPM	267.65
H1b + H2a: spatial EBPM > TBPM	4.57
H1b + H2b: spatial EBPM = TBPM	657.09
H1b + H2b + H H3a: OT profit EBPM > TBPM	30.54
H1b + H2b + H3b: OT trade-off TBPM, not EBPM	134.9
H1b + H2b + H3c: OT effect EBPM = TBPM	1,228.06
additional null-model	18,178,038.00

Note. TBPM = time-based prospective memory, EBPM = event-based prospective memory, OT = ongoing task performance

Hypothesis 1b received more support than hypothesis 1a. This means that it is more likely that sequential processes (verbal attention and working memory, temporal episodic working memory, time perception and monitoring) are equally involved in TBPM and EBPM, rather than that they are differentially involved in TBPM and EBPM. The Bayes factor of hypothesis 1a is greater than 1, which indicates that this model is also partially supported by the data.

Hypothesis H1b in combination with H2a received more support than in combination with H2b. The idea that spatial processes (visuospatial attention and working memory, and spatial episodic working memory) are more involved in EBPM than in TBPM, as stated in hypothesis 2a, received less support than hypothesis 2b, which states that there is no difference in the involvement of spatial processes in EBPM and TBPM.

Hypothesis 3c received more support than hypotheses 3a and 3b. It is more likely that there is no difference in the influence of ongoing task performance on TBPM and EBPM, than that there would be such a difference. Compared to the idea that there is no differential influence of ongoing task performance on EBPM or TBPM, there is less support for the hypothesis that there is a tradeoff between TBPM (and not EBPM) performance and ongoing task performance, or the hypothesis that better ongoing task behavior is related to better EBPM performance and less so for TBPM.

The additional null-hypothesis received overwhelming support. The models that were formulated based on theoretical reasoning did not explain the current data better than the alternative model that stated all regression coefficients linking the predictors with the two outcome variables (TBPM and EBPM) equal zero. None of the hypotheses that were evaluated thus received support over the null hypothesis.

Additional exploratory analyses

Binary logistic regression analyses

After finding no support for the theory-driven models that were initially formulated, data were further explored to examine the contribution of individual predictors on EBPM and TBPM. As opposed to the Bayesian approach, where theories were evaluated formulating specific hypotheses on the relative contribution of several combined predictors on EBPM versus TBPM, here we explored the data bottom-up, by binary logistic regression analyses. A forward stepwise method was used (likelihood ratio), in congruence with the exploratory nature of this analysis.

The dependent variables were binary: optimal or suboptimal EBPM and TBPM performance. All eight predictors were entered into the model in the first step: Visuospatial attention and working memory, verbal attention and working memory, spatial episodic working memory, temporal episodic working memory, time perception, time comparison, monitoring behavior, and ongoing task performance. These were all continuous variables. Note that in contrast with the Bayesian approach, no specific expectations were formulated on what predictors would contribute to either dependent variable.

For EBPM, 71 of 102 participants performed suboptimal (<100% correct), and 31 optimal (100% correct).

The Wald criterion demonstrated that of the included variables, only ongoing task performance made a significant contribution to the prediction ($p < .05$). Better ongoing task performance decreased likelihood of optimal EBPM performance (see table 5), possibly reflecting a trade-off effect. The full model predicted optimal EBPM performance 73% correctly, but not significantly better than the constant only model (70% correct).

Table 5 Logistic regression statistics for EBPM

		95% CI for Odds ratio		
	B(SE)	**Lower**	**Odds ratio**	**Upper**
Included				
Constant	3.377(1.731)			
Ongoing task performance	-.004(0.002)*	0.993	0.996	0.999

Note. EBPM = event-based prospective memory. R^2= .06 (Cox & Snell), .08 (Nagelkerke). Model $\chi^2(1) = 6.174$, p = .013. * p <.05.

Table 6 Logistic regression statistics for TBPM

		95% CI for Odds ratio		
	B(SE)	**Lower**	**Odds ratio**	**Upper**
Included				
Constant	-8.06(1.66)			
Verbal working memory	0.03(0.01)**	1.01	1.03	1.05
Time perception	-0.78(0.31)*	0.25	0.46	0.84
Monitoring behavior	0.20(0.05)**	1.11	1.22	1.33

Note. EBPM = event-based prospective memory. R^2= .36 (Cox & Snell), .52 (Nagelkerke). Model $\chi^2(3) = 46.087$, $p < .001$. * p <.05, ** $p < .001$.

For TBPM, 73 of 102 participants performed suboptimal (<100% correct), and 29 optimal (100% correct). The Wald criterion demonstrated that verbal working memory, time perception and monitoring made a significant contribution to the prediction ($p < .05$). Better performance on these variables increased likelihood of optimal TBPM performance. The full model predicted optimal TBPM performance 81% correctly, significantly better than the constant only model (72% correct).

The results of these logistic regression analyses suggest several predictor variables to be relevant for PM performance.

3.3.2 Patterns of performance

The patterns of performance for different participants show double dissociations between performance on EBPM versus TBPM (see table 7). Although most participants performed suboptimal on both measures and some performed optimal on both TBPM and EBPM, a considerable proportion of participants performed optimal on one, and suboptimal on the other measure. These patterns are indicative for the discriminative ability of these measures of EBPM and TBPM.

Table 7 Dissociations between EBPM and TPBM

group	N
EBPM optimal, TBPM suboptimal	20
TBPM optimal, EBPM suboptimal	18
both optimal	11
both suboptimal	53
total	*102*

Note. EBPM = event-based prospective memory. TBPM = time-based prospective memory. Optimal = 100% correct, suboptimal <100% correct.

Multivariate analysis of variance (MANOVA)

Based on the dissociations in performance on EBPM and TBPM, groups of participants were defined and compared on those variables that were used to predict EBPM and TBPM performance in the main analyses (see table 1 for a description of the included variables and table 7 for definition of the groups). Even though no differential results became apparent using a confirmative approach, it is possible that dissociations would exist, only not in the exact way that was hypothesized using the Bayesian model selection approach. Differences in means on these variables between groups could indicate functional dissociability of EBPM and TBPM, in the sense that cognitive processes are differentially associated with either type of PM. These exploratory analyses were used to search for possibly interesting data patterns that could be used for developing new hypotheses based on the current data, to be performed in follow-up studies.

Using Pillai's Trace, there was a significant group effect, $V = 0.52$, $F(24,279) = 2.44$, $p < .001$. It should be noted however that the assumption of homogeneity was violated, as the test for equality of the covariance matrices was significant (Box's M = 198.08, $p = .003$). Also, error variances were not equal across groups for the variable 'monitoring behavior', as shown by Levene's test of equality, $F(3,98) = 2.49$, $p < .05$. All other error variances were not significantly different across groups.

To investigate on what variables the groups differed, separate univariate ANOVAs were performed (see figure 3) and these revealed significant effects for verbal working memory, $F(3,98) = 3.24$, $p < .05$, and time monitoring $F(3,98) = 12.66$, $p < .001$. Group comparisons for time perception, $F(3,98) = 2.19$, $p = .094$, and ongoing task performance $F(3,98) = 2.15$, $p = .099$ might be considered as trends towards significance, however they did not reach the criterion for significance. No significant differences were found for visuospatial attention and working memory, spatial episodic working memory, temporal episodic working memory and time comparison ($p > .1$) either.

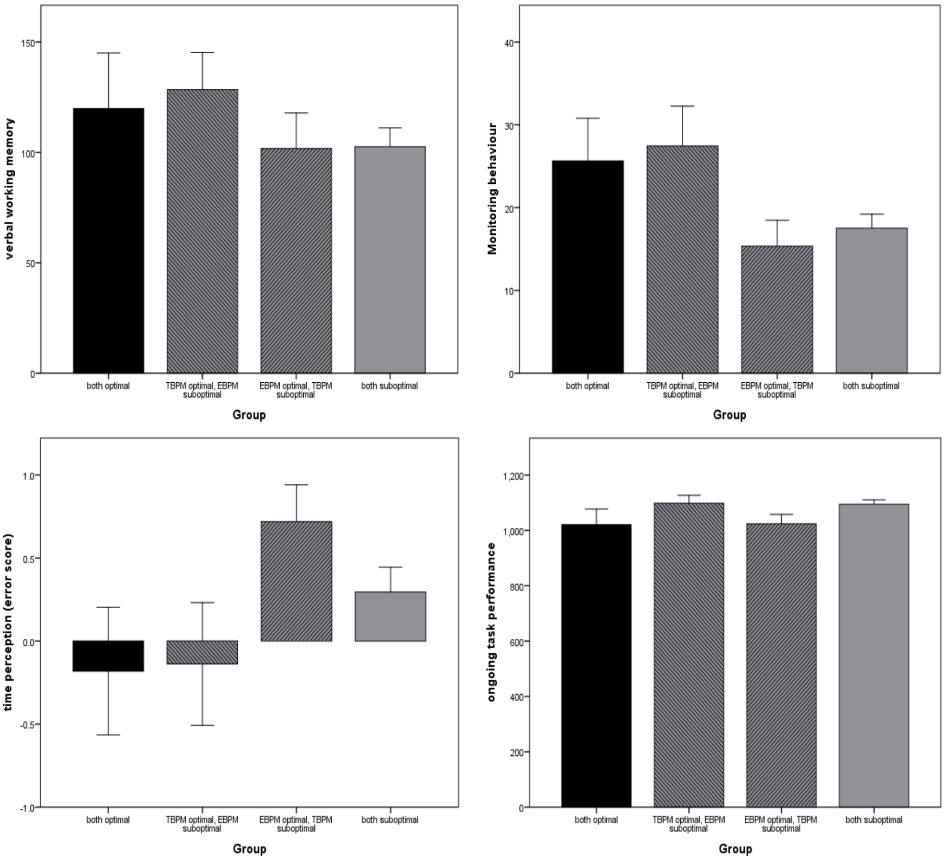

Figure 3. *Differences between groups. Error bars represent +/- 2SE.*

This means that groups of participants who performed optimal on EBPM but suboptimal on TBPM and vice versa, those who performed optimal on both and those who performed suboptimal on both EBPM and TBPM differed in their performance on two of the variables, indicating functional differences between these groups. T-tests were

subsequently performed to detect which groups differed and in what direction. Differences between groups could indicate differential involvement of cognitive processes in EBPM versus TBPM.

Verbal working memory performance was significantly better in the group of participants with optimal TBPM and suboptimal EBPM performance than in the groups with optimal EBPM and suboptimal TBPM performance, $t(36) = -2.29$, $p < .05$, and those with suboptimal performance on both measures, $t(69) = 2.93$, $p < .05$.

Participants with optimal performance on TBPM and suboptimal on EBPM showed more active monitoring behavior as compared to participants with optimal EBPM and suboptimal TBPM performance, $t(36) = -4.29$, $p < .001$, and those with suboptimal performance on both measures, $t(21) = 3.89$, $p = .001$. Participants with optimal performance on both measures also showed more active monitoring than participants with optimal EBPM and suboptimal TBPM performance, $t(29) = -3.62$, $p = .001$, and those with suboptimal performance on both measures, $t(62) = 3.71$, $p < .001$.This indicates that groups of participants who specifically perform well at TBPM, show better verbal working memory performance and more active monitoring behavior than those who perform specifically well at EBPM or suboptimal on both measures.

Descriptives of the variables with (possible trends towards) significant group differences are shown in table 8.

Table 8 Descriptives of the variables with (possible trends towards) significant differences between groups

	group mean (SE)			
	both optimal	**optimal TBPM, suboptimal EBPM**	**optimal EBPM, suboptimal TBPM**	**both suboptimal**
verbal working memory*	119.91 (12.60)	128.44 (8.44)	101.80 (8.04)	102.55 (4.28)
monitoring behavior*	25.64 (2.58)	27.44 (2.41)	15.35 (1.57)	17.51 (0.85)
time perception~	-0.18 (1.27)	-0.14 (1.57)	0.72 (0.99)	0.30 (1.09)
ongoing task performance~	1021.09 (185.61)	1098.22 (120.28)	1023.65 (152.27)	1094.55 (116.46)

Note. *$p < .05$, ~$p < .1$.

Discussion

While the body of knowledge regarding prospective memory (PM) functioning is growing, new questions have arisen about the cognitive components underlying PM. In the current study, we aimed to check assumptions derived from the accumulating body of

research on PM. Ideas derived from data-driven theories were tested using confirmative statistics. Most of the leading theories currently assume that multiple processes are involved in PM, with differences in their contribution depending on the type of task and/or daily life situation (a.o. McDaniel & Einstein, 2000; Scullin, McDaniel & Shelton, 2013). These assumptions were translated into Bayesian hypotheses about the differential contribution of different (cognitive) processes to different types of PM.

First, the idea was tested that sequential processes are more involved in situations where an action was to be performed at a specific moment in time (time-based: TBPM), than when the action was linked to a specific event (event-based: EBPM). Especially monitoring and estimating the passage of time are commonly associated with TBPM (e.g. Mäntylä et al., 2007), and conceptually they are easily linked. Surprisingly, there was more support for the alternative hypothesis that predicted equal contribution of these processes to TBPM and EBPM.

Furthermore, all other hypotheses that predicted equal contribution of cognitive processes on TBPM and EBPM received more support than those that predicted differences. One of these was based on a leading assumption that provides an explanation for differences in PM performance: the concept of *focality*. It states that automatic retrieval occurs in EBPM tasks when the ongoing task overlaps with the external cue, requiring few resources (Rose et al., 2010). Performing a TBPM task does require effortful processing, as no external cue is involved. Trade-off effects thus were expected between the ongoing task and TBPM, not EBPM. Our data did not fit this assumption. One alternative hypothesis stated that overall vigilance facilitates detection of an external PM cue and thus a positive effect was expected of ongoing task performance on EBPM, more than for TBPM (lacking an external cue). This hypothesis did not receive support either. The alternative hypothesis that presumed no differential effects of ongoing task performance on TBPM and EBPM was best supported by the data.

Models that proposed a contribution of spatial processes to PM received little support; models that excluded these processes showed a better fit. It is therefore probable that these processes are not relevant for (this operationalization of) PM. In sum, the data did not confirm the predictions that were formulated based on current theories on PM.

On basis of the foregoing one might conclude that EBPM and TBPM involve the same cognitive processes. However, the addition of an extra null-model showed more support for the hypothesis that none of the included variables contributed to either type of PM. This result could either mean that existing theories of PM are not valid, or that the hypotheses derived from these theories were not formulated correctly. Either

way, it indicates that current models of PM are not clearly framed yet. Therefore, we refrained from drawing firm conclusions about the validity of the theories that were under investigation.

In contrast with the confirmatory Bayesian approach, additional exploratory analyses did show significant contributions of individual predictors to EBPM and TBPM. A possible trade-off effect was found between ongoing task performance and EBPM performance. Verbal working memory, time perception and monitoring behavior were shown to be related to TBPM performance. Also, dissociations were found between participants in their performance on the EBPM and TBPM tasks, indicating discriminative ability of these measures. This outcome means that the task that was used to operationalize PM was able to distinguish between different types of PM, even though these were tested in parallel.

Furthermore, performance on several cognitive measures differed between groups of participants who performed optimal on TBPM and suboptimal on EBPM and vice versa. This finding is in congruence with another study from our group (Kant et al., 2014) where the same paradigm was used in stroke patients and differential contribution of cognitive processes was found as well. In the current study, differential effects on PM performance were found for monitoring and verbal working memory. Monitoring is intrinsically more related to TBPM than to EBPM, and therefore it is not surprising that more active monitoring was shown in participants who performed well on TBPM as compared to those who did not. Verbal working memory was also better in participants who performed better on TBPM than on EBPM, compared to those participants who showed the opposite pattern, and those who showed suboptimal performance both on EBPM and TBPM. Verbal working memory is a sequential process and therefore this result would be fitting with the sequencing hypothesis, although other sequential processes included in the analyses did not show the same effect.

From the preceding exploratory data-driven analyses it appears that there is a functional dissociation between EBPM and TBPM nonetheless, even when the specific theoretical models that were tested could not be confirmed. The two main types of PM were shown to be dissociable, but apparently not in the way that was formulated a priori based on theoretical assumptions. Using the stringent method of Bayesian model selection, specific assumptions about relations between several variables were tested and found to be not supported in the data analysis. It is possible that the nature of distinctions in PM is different from the currently hypothesized relations between these specific (groups of) variables.

When speculating a posteriori about the implication of these results, one striking finding that raises questions about current theories is the relation between ongoing task performance and PM performance. This relation may not be as straightforward as previously thought. Based on the concept of *focality,* as part of the multi-process framework, one would not expect a trade-off effect for *focal* EBPM tasks. However, we did find that participants who performed better at the EBPM task, showed worse ongoing task performance. A possible explanation may involve the different impacts ongoing task (OT) accuracy and OT speed yield. Although the detection of the PM cue may be facilitated by overlap with the OT, performance on the OT may suffer from the time it takes to perform the (*focal*) EBPM task. To translate this to daily life: when on your way home you want to buy milk at the supermarket, and stop the car when you pass by, you lose time on your commute. So, when speed enters the equation and not only accuracy, the outcome may differ. This could explain why no support was found for the posed hypotheses on the role of OT performance.

One other factor of interest may be the role of timing in TBPM. More active monitoring was shown to be related to better TBPM performance. However, no support was found for the overall sequencing model, also including time perception and verbal working memory. What cognitive processes underlie adequate timing in TBPM thus remains unsettled.

The current study contributes to the discussion on what composes PM. One of the strengths of our approach is the stringent statistical method that was used. Confirmative statistics force formulation of specific expectations. Assumptions that are otherwise easily taken for granted were now explicitly tested. With this approach, the building blocks underlying PM were thoroughly inspected. Assumptions logically derived from leading theories, among others about relevant differences in task characteristics, proved not to be easily confirmed. The use of confirmative statistics prevented a confirmation bias in favour of results that are congruent with existing theories as opposed to contradictory results. Models based on leading theories about PM could not explain the data, and the statistical approach that was used helped to highlight the need to critically review these.

Follow-up analyses were used to explore interesting patterns in the data as input to form new theories and generate future hypotheses. Conclusions from these analyses should be drawn with caution, as they were not tested using specific a priori stated hypotheses. A positive result may therefore be given too much weight, whereas a null-result could be disregarded.

Taken together, the current results clearly ask for further development of PM theories, whilst not discarding existing PM theories. Hypotheses on the involved cognitive operations were not supported when tested using a stringent theory-driven approach: Bayesian model selection. A more liberal, explorative analysis did show that functional dissociations in PM exist. This methodological endeavor suggests the relevance of investigating the PM construct further at a theoretical level and the usefulness of carrying out more confirmatory studies evaluating existing ideas on PM. For example, the concept of *focality* could be further evaluated. Numerous papers about *focality* have been published (e.g. Scullin, McDaniel & Einstein, 2010; McDaniel & Einstein, 2007), mostly exploratory in methodology. The present study was a first attempt to confirm the concepts that have emerged, by applying the idea of *focality* to explain hypothesized differences in event- versus time-based PM. However, assumptions about effortful versus automatic processing could not be confirmed. A possible follow-up could be to apply the same confirmatory statistical approaches to test assumptions with respect to *focality* in different types of EBPM, as we did not include a comparison between *focal* and non-*focal* EBPM tasks in the current study.

Also, future studies could be directed towards what cognitive processes underlie monitoring of time in TBPM. It is obvious that temporal processing would be necessary to adequately perform a TBPM task, but as there is not a specific sensory system for time in the brain, other cognitive functions are expected to be recruited. It remains to be investigated what mechanisms are involved here.

Further attempts to explain differences in PM processing such as those that we found, may lead to increased understanding of the cognitive architecture of PM, eventually leading to a firmer theoretical framework.

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5

Dissociations between Spatial and Temporal Order Memory: a Neuropsychological Patient Study

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Abstract

Objective: In complex real life situations, memories for temporal and spatial information are naturally linked since sequential events coincide in time and space. Whether this connection is inseparable or instead whether these processes are functionally dissociable was investigated in this patient study.

Method: Spatial object-location and temporal order memory tasks were administered to 36 stroke patients and 44 healthy control participants.

Results: On group level, patients with a stroke in the left hemisphere performed worse on temporal order memory, compared to the control participants. On individual level, using a multiple case-study approach, a clear pattern of dissociations was found between memory for temporal and for spatial features.

Conclusions: These findings indicate that location and temporal order memory contain functionally separable processes. This adds to our understanding of how context information is processed in human memory.

Introduction

Human memory for temporal and spatial context information is naturally linked in daily life. Sequential events tend to coincide in time and space. When memorizing a route, locations and the order in which these are perceived are integrated and retrieved from memory simultaneously. Remembering a specific event you experienced (episodic memory) typically involves remembering not only the content ('what'), but also a spatiotemporal context: 'where and when' (see a.o. Healy, Cunningham, Gesi, Till & Bourne, 1991). Recent studies have demonstrated the existence of dedicated neural mechanisms for integrating spatial and temporal information (Howard & Eichenbaum, 2014). Despite their natural connection, there are several indications of separate processing mechanisms for spatial and temporal order information in episodic memory. Van Asselen, Van der Lubbe and Postma (2006) showed that encoding of the location and temporal order is not obligatory. In this study, we set out to dissociate these two highly relevant aspects of contextual episodic memory, directly comparing retrieval of very recent visual information for temporal order and spatial location in a parallel paradigm. One can assume that the 'episodic buffer' is mainly recruited here, a system in the most well-known model of human working memory that is capable of binding contextual information (Baddeley, 2000).

Previous neuroimaging and neuropsychological studies have globally sketched the neural circuitry of spatial and temporal order memory separately. Brain regions that are probably involved in spatial (working) memory are the dorsolateral prefrontal cortex, posterior parietal cortex and hippocampal formation (Kessels et al., 2000a; Constantinidis & Wang, 2004; Friedman & Goldman-Rakic, 1994; Glabus et al., 2003; Inoue, Mikami, Ando & Tskukada, 2004), specifically in the right hemisphere (Feigenbaum, Polkey & Morris, 1996; Miotto, Bullock, Polkey & Morris, 1996; Nelson et al., 2000). Temporal order memory has been associated with activity in the prefrontal cortex and temporo-parietal junction (Zhang et al., 2004; Van Asselen et al., 2006). Kessels, Hobbel and Postma (2007) investigated age-related decline in spatial and temporal order episodic memory. They speculate that the left hemisphere may be more involved in temporal order memory, and that the right hemisphere is more critical for spatial order memory. Binding contextual features has been related to prefrontal activation and a hippocampal-diencephalic 'binding circuit'. Dissociations between these processes however, have not been directly tested thus far.

The specific contextual features of location and temporal order are relevant to study as they are typically combined in many activities, such as route learning, and dysfunctioning of these processes due to brain damage can have significant impact on daily life

and cause cognitive complaints (Van der Ham et al., 2010). Importantly, the behavioral patterns observed in stroke patients can provide invaluable insights in the extent to which temporal order and spatial object location and the binding of these features in episodic memory are functionally dissociable. Whereas in Korsakoff patients binding problems seem most prominent (Postma et al, 2006), in the stroke population, with focal lesions and heterogeneous in terms of localization, differential patterns can be expected.

Stroke patients comprise an ideal population to study dissociations in cognitive processes because of their heterogeneity with respect to lesion location, which allows for broad exploration of patterns of cognitive functioning. There is evidence that different types of contextual features in episodic memory and binding of those features can be affected by stroke (Kessels, Kappelle, de Haan, & Postma, 2002). Also, temporal order memory can be affected in stroke patients (Schoo et al., 2014). Moreover, Van Geldorp, Kessels and Hendriks (2013) studied target and location memory in stroke patients. They found problems in both types of memory, but not in binding context with content. In contrast, Postma et al. (2006) found that Korsakoff patients showed problems particularly in binding contextual features. Importantly, a direct comparison between spatial and temporal order memory has not been performed in stroke patients.

The rationale for the current study was to investigate functional dissociations between different relevant dimensions of contextual memory, by directly comparing performance on temporal order versus spatial location and binding of those features in memory, and how these aspects can be differentially affected following focal neurological damage. Problems in separate contextual attributes might be expected, and/or specifically in binding those features together, depending on site of lesion.

In addition to the investigation of functional dissociations, observed patterns of lesion localization were used to search for convergent evidence of separate neural networks that underlie spatial and temporal order memory and binding of spatial and temporal features.

As an important global neural difference between spatial and temporal order memory is thought to involve hemispheric lateralization, dissociations in task performance of patients with left, right and bilateral lesions were investigated. Moreover, individual patterns of performance were investigated and patients' performance was related to localization of lesion. Patients with deficits in temporal order memory were expected to have lesions in frontal regions, possibly with left lateralization. Spatial location memory deficits were expected to be related to right hemisphere lesions, in frontal as well as

temporal and parietal regions. Binding problems could be related to frontal and (medial) temporal damage.

By testing how performance on spatial and temporal order memory and binding of those features changes following stroke, we aimed to better understand these processes.

Method

Participants

From the University Medical Center Utrecht (UMCU) 36 patients were recruited with diagnosis of stroke based on clinical assessment and confirmed by imaging (CT, MRI), in accordance with inclusion regulations described in UMCU Medical Ethical Committee protocol 05-109. Exclusion criteria were diagnosed comorbid psychiatric or neurological diseases and conditions (such as dementia, as derived from the medical charts of the patients) and pre-existing impairments that would limit completion of the assessment (such as blindness). Practice conditions of the experimental procedure were used to detect whether there were any confounding (stroke-related) factors, such as neglect, that would hamper task performance to such an extent that a patient could not follow the experimental procedure.

Location of lesion was confirmed by an experienced neurologist (CJMF), using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans that were obtained according to clinical practice. All available scans were used to determine the ultimate structural damage as exactly as possible, using a human brain atlas as reference (Duvernoy, 1999).

Forty-four age- and education-matched people without self-reported neurological or psychiatric disorders served as control participants. These participants were either spouses or family of patients or volunteers who came to our attention through word of mouth. Participants were treated in accordance with the Declaration of Helsinki.

Materials

Educational level was coded according to Verhage and Van der Werff (1983), range 1 through 7 from less than primary school to university degree. Intelligence (premorbid) was estimated using the Dutch version of the National Adult Reading Test, scores corrected for age and gender (Schmand, Bakker, Saan & Louman, 1991). Dexterity was assessed using the Annett Handedness Inventory (Annett, 2004).

Screening Tasks

The neuropsychological screening battery included standardized tests that measured reasoning ability, (working)memory and attention/executive functioning.

Abstract reasoning was measured by the Raven Advanced Progressive Matrices Short Form (Arthur & Day, 1994). The Dutch version of the Rey Auditory Verbal Learning Test (Saan R.J. & Deelman, 1986) was administered to measure verbal learning, delayed recall and recognition memory. To assess verbal working memory, the Letter Number Sequencing task was used (a subtest of the Wechsler Adult Intelligence Scale III, Wechsler, 1997). Visuospatial working memory was measured with the Corsi-Block task (Kessels, Van Zandvoort, Postma, Kappelle & de Haan, 2000b). Attention/executive functioning was measured by the Trail Making Test parts A and B (Reitan & Wolfson, 1992).

Experimental Tasks

To assess spatial and temporal order memory and binding of these features, an object relocation paradigm was used that has shown to be able to differentiate between various memory aspects and is sensitive to differences between clinical groups (Van Asselen et al., 2006; Postma, Van Asselen, Keuper, Wester & Kessels, 2006). Experimental procedures and stimulus materials were largely adapted from Postma et al. (2006). The paradigm allowed for comparison between recall for single features (spatial location versus temporal order) as well as combined recall of both features together (spatio-temporal binding). Subjects were asked to either remember the location of objects presented visually on a computer screen, or the order of appearance, or both.

The tasks were designed to suit the specific demands that are involved in patient studies, keeping speed, information load and other general processing demands as low as possible. The experiment was designed using Object Relocation© software (Kessels, Postma & De Haan, 1999). Stimuli were colored pictures of highly familiar objects that were presented in a 19 x 19 cm square frame centered on a gray background screen on a 17" touch-sensitive LCD monitor (ELO Accutouch®, resolution= 1024x768, viewing distance = 65 cm). Average stimulus size was 1 x 1 cm. Stimuli were never reused in the experiment.

Two task conditions served as practice and allowed participants to familiarize themselves with the procedure. Only if participants were able to perform the experimental procedure correctly (i.e. sufficient motor function for using the computer with touch-screen, sufficient comprehension, attentional capacity and perceptual ability to replace all objects following instructions), the five experimental conditions were administered.

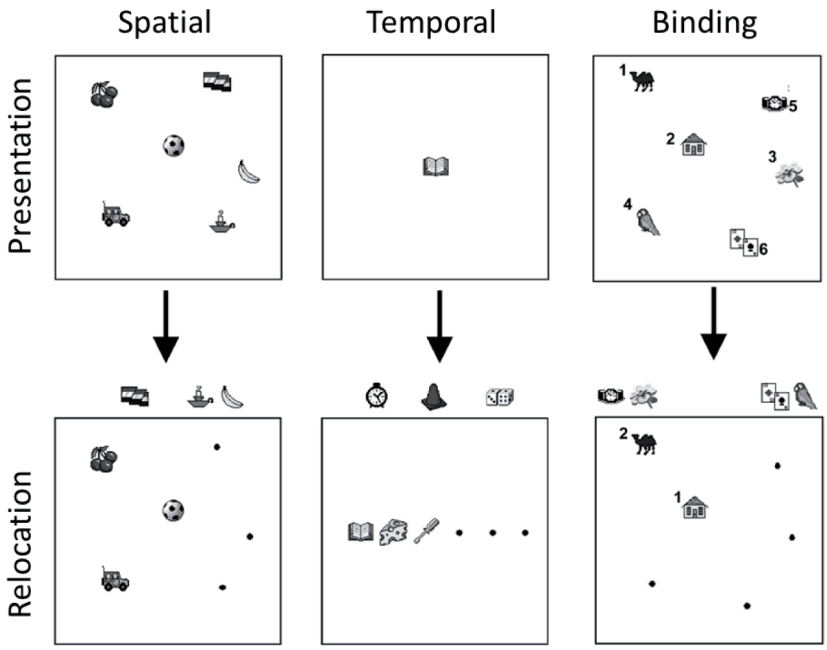

Figure 1. *Stimulus materials. Examples of spatial and temporal task conditions and the combined condition (binding). The digits were never shown but are used here to indicate the order of presentation and recall.*

One practice run preceded each experimental condition (containing two trials). The recall phase posed no time restrictions.

In the first experimental condition (purely temporal), six objects were shown serially, each object for three seconds, always in the middle. Next, participants were instructed to place the objects in the correct temporal order on a one-dimensional horizontal array of six dots, i.e. the leftmost dot should be assigned the object that was presented first and the rightmost dot should be assigned the last shown item.

In the second experimental condition (purely spatial), six objects were shown simultaneously for 18 seconds, at different locations. Next, participants were instructed to relocate the objects to their correct positions, which were marked by black dots in the square frame.

In the third experimental condition (spatiotemporal presentation – temporal order recall), six objects were shown serially for 3 seconds, each at a different location. Next, participants had to arrange the objects in their correct temporal order.

In the fourth experimental condition (spatiotemporal presentation – spatial order recall), presentation was identical to the previous condition, but participants relocated the objects to their correct position.

In the fifth experimental condition (fully combined), presentation was similar to that of the previous two conditions. In the recall phase, objects were to be placed at their correct location in the correct temporal order.

The conditions as described above were adapted from other studies used for different purposes (e.g. Van Asselen, Van der Lubbe & Postma, 2006). Of interest here was to contrast single feature recall (spatial location versus temporal order) and combined spatiotemporal recall. To this aim, and to simplify statistical analysis by minimizing the amount of between group comparisons and thereby decreasing risks of chance capitalization, three main outcome measures were calculated: spatial location, temporal order and binding. For each experimental condition, the percentage of incorrectly relocated objects was calculated. This "percentage incorrect" per condition was averaged across the two experimental conditions for each feature (i.e. temporal order was calculated by averaging performance on the first and third condition, spatial location by averaging the second and fourth condition). To obtain a measure of binding spatial and temporal features, the percentage incorrect was calculated for the fifth, fully combined, condition. A score of 100% incorrect in combined recall signified that both spatial and temporal relocation were 100% incorrect.

Data analysis

Group differences

Group differences between patients and control participants' demographical variables and neuropsychological task performance were tested using chi-square tests (gender, dexterity), Mann-Whitney U (educational level), two-tailed independent t-tests (age, IQ) and multivariate analyses of (co)variances, controlling for gender and age (screening tasks). Bonferroni correction was applied for the screening tasks, resulting in adjusted criterion levels for significance of $p < .005$ and .0001.

To investigate overall differences between groups (control participants, and left, right and bilateral stroke patients) on the experimental task conditions (spatial location memory, temporal order memory and binding) a multivariate analysis of (co)variance was performed, with age and gender as covariates. Post-hoc univariate ANOVAs and t-tests were performed to investigate which groups differed on which variables.

Potential ceiling and floor effects were tested by comparing mean group performance on each condition to minimum and maximum level (0% and 100% incorrect) using one-tailed independent t-tests.

Individual patterns

Because of heterogeneity of the patient group in terms of lesion location, a case study approach was used to investigate individual patterns of performance and dissociations with respect to lesion location. Statistical procedures by Crawford (Crawford, Howell & Garthwaite, 1998; Crawford & Howell, 1998; Crawford & Garthwaite, 2002) were applied. Using these methods, single test scores were compared with norms derived from the control sample, to make an appropriate parametric statistical analysis of possible deficits. Essentially, this method is a modified independent samples t-test in which the individual is treated as a sample of N = 1. For the current study, the program "BTD_cov" was used: the Bayesian test for a deficit in a single case controlling for covariates, as described by Crawford, Garthwaite and Ryan (2011). Abnormalities of patients' scores on spatial versus temporal order memory, and binding, were tested, correcting for age.

Patterns of deficits on the experimental tasks were explored in relation to standard neuropsychological performance (based on existing normative data) and site of lesion.

Results

Demographical data and patient characteristics

Table 1 shows that control participants did not differ from the patients with respect to level of education, (premorbid) intelligence, dexterity, and age, but were more often female than the stroke patients. Stroke is more prevalent in males (Wilson, 2013), and control participants typically included spouses and family members from the opposite sex. Potential influence of gender was therefore examined in the primary group analyses.

Indications of stroke severity in terms of impact on activities in daily living (ADL) were derived from medical status at time of discharge. Barthel Index (Mahoney & Barthel, 1965) scores were estimated for each patient. For 21 out of the 36 patients (58%), no significant ADL limitations were reported. The remaining 15 patients (42%) were mildly dependent in functional ability at time of discharge. Mean stay on the neurology unit was 12 days (SD = 11). Destination of discharge was unknown for 1 patient, home for 58% of the patients (n = 21), and a rehabilitation centre for 10 patients (28%). Four patients (11%) were admitted elsewhere (to a hospital or residential care facility). Duration

Table 1 Patient and Control Participant Demographics and Performance on Screening Tasks

Variable	Patients *N = 36*	Control participants *N = 44*	Significance *p*	Effect size
Gender (% male)	69 %	36 %	.003°	φ = -.329
Dexterity (% righthanded)	74 %	75 %	.883	φ = .017
Educational level (median, IQR)	5 (5-6)	6 (5-6)	.623	*r* = -.055
Age (M ± SD)	57.1 ± 14.1	55.4 ± 16.8	.615	*r* = .057
IQ (M ± SD)	107.9 ± 18.0	106.6 ± 14.2	.715	*r* = .042
Raven Matrices	7.3 ± 3.3	8.9 ± 2.2	.0009*	η_p^2 = .205
RAVLT immediate recall	40.7 ± 12.3	49.3 ± 11.2	<.0001**	η_p^2 = .274
RAVLT delayed recall	8.6 ± 4.0	10.6 ± 3.5	<.0001**	η_p^2 = .279
RAVLT delayed recognition	27.4 ± 3.8	29.3 ± 1.3	.0020*	η_p^2 = .187
TMT A time	46.8 ± 23.5	33.0 ± 14.5	.0001*	η_p^2 = .269
TMT B time	111.4 ± 87.4	69.8 ± 29.3	.0002*	η_p^2 = .236
TMT index	2.4 ± 1.1	2.3 ± 1.0	.7548	η_p^2 = .017
Letter Number Sequencing	8.7 ± 3.5	10.9 ± 2.8	.0003*	η_p^2 = .234
Corsi forward score	7.7 ± 1.4	8.2 ± 1.9	.0023*	η_p^2 = .183
Corsi backward score	7.5 ± 2.1	8.8 ± 2.2	.0001*	η_p^2 = .253

Note. Group differences between patients and control participants were tested using chi-square tests (gender, dexterity), Mann-Whitney U (educational level), two-tailed independent t-tests (age, IQ) and multivariate analyses of variances, controlling for gender and age (screening tasks). RAVLT: Dutch version of the Rey Auditory Verbal Learning Test; TMT: Trail Making Test. *°p < .05,*p < .005, **p < .0001* (Bonferroni correction for multiple comparisons was applied for the screening tasks)

of hospital admission, discharge destination and estimated stroke severity did not differ significantly across patient groups. Barthel Index scores were significantly correlated to the experimental variables. However, they did not explain group differences.

In the patient group, ischaemic strokes predominated (28% haemorrhagic). Average interval between date of stroke and testing was 17 months (*SD* = 8.2). Time between the index event and scanning varied, with a median of 5 days (interquartile range 1-18, when no infarction was visible on day 0 follow-up scans were used to confirm location of lesion). No influence of elapsed time between event and test date or between event and date of most recent scan was found on any variable. For 12 patients only CT scans were available. Lesion locations in patients were widespread throughout the brain; 16 patients had strokes in the right hemisphere, 12 in the left, and 8 showed bilateral damage. Two patients had a history of a previous stroke.

Table 1 shows that patients on average scored worse than control participants on all neuropsychological measures, except the TMT index score (divided attention) and IQ.

Main analyses

Group differences

Performance on spatial and temporal order memory and binding of spatial and temporal features was compared between groups In table 2, performance of each group (control participants, bilateral, right and left hemisphere stroke patients) on the experimental variables is shown.

Table 2 Analyses of Variance in Object Relocation Task Performance Across Groups

Condition	Group		Errorscore	Range	Significance	Effect size	Power
		n	**Mean *(SD)***	**(Min-max)**	***p***	***partial* η^2**	
spatial location	control	44	14.47 *(12.85)*	0-58.50	.715	.018	.137
	left	12	22.35 *(21.55)*	0-67			
	right	16	16.18 *(14.50)*	0-46			
	bilateral	8	19.29 *(26.46)*	0-79.50			
temporal order	control	44	17.17 *(17.00)*	0-62.50	.010*	.140	.822
	left	12	36.85 *(26.37)*	0-71			
	right	16	19.04 *(14.67)*	0-41.67			
	bilateral	8	16.15 *(12.68)*	0-33.50			
binding	control	44	64.48 *(26.97)*	0-100	.210	.059	.391
	left	12	69.83 *(34.07)*	0-100			
	right	16	62.50 *(27.37)*	0-100			
	bilateral	8	85.75 *(16.01)*	56-100			

Note. *$p < .05$

The assumption of homogeneity was met, as the test for equality of the covariance matrices was not significant (Box's M = 44.48, $p > .05$). However, error variances were not equal across groups for the variable 'spatial location memory', as shown by Levene's test of equality, $F(7,72) = 4.00$, $p = .001$. Error variances for 'temporal order memory' and 'binding' were not significantly different across groups ($p > .05$).

Using Pillai's Trace, there was a significant overall group effect, $V = .23$, $F(9,222) = 2.05$, $p = .036$. Effect size $\eta_p^2 = .077$, observed Power = .857. The covariate age significantly affected the outcome variables ($F(3,72) = 12.34$, $p < .001$, effect size $\eta_p^2 = .340$, observed Power = 1). The effect of gender was not significant ($F(3,72 = 1.67$, $p = .178$, effect size $\eta_p^2 = .066$, observed Power = .424).

In addition, using a general linear model with group and gender as between subjects factors, and experimental task condition as within subjects factor, no significant effects of gender were detected (spatial location $p = .562$, $\eta_p^2 = .005$; temporal order $p = .828$, $\eta_p^2 = .001$; binding $p = .930$, $\eta_p^2 < .001$), and no interaction effects between gender and group either ($p > .05$)."

To investigate for which variables the groups differed, separate univariate ANOVAs on the outcome variables were performed. These revealed significant effects for temporal order memory ($F(3,76) = 4.02$, $p = .010$, $\eta^2 = .137$), but not for spatial location memory ($F(3,76) = 0.82$, $p = .487$, $\eta^2 = 0.031$) and binding ($F(3,76) = 1.56$, $p = .206$, $\eta^2 = .058$), see table 2. Post-hoc Bonferroni-corrected pairwise comparisons show significantly lower scores for temporal order memory in left-hemisphere stroke patients compared with control participants ($p = .014$, $r = 0.913$) and bilateral stroke patients ($p = .047$, $r = 0.886$), but not compared with right-hemisphere stroke patients ($p = .633$, $r = 0.760$). Patients with bilateral or right hemispheric lesions did not perform worse than control participants ($p > .05$).

All participants were able to perform the tasks according to procedure. No significant ceiling or floor effects were found on any condition, as mean performance was significantly different from 0% and 100% ($p < .05$) in both patients and control participants. However, the scores were not normally distributed (Kolmogorov-Smirnov and Shapiro-Wilk tests $p < .001$).

Crawford statistics

Each individual patient's scores on spatial location, temporal order memory and binding were compared to the control participants group performance, controlling for age. Seven patients (18%) obtained abnormal scores (see table 3, and supplementary material for test statistics).

Patterns of performance

Three patients showed deficits in spatial location memory, but not in temporal order memory (MS, DG and LS), one of whom (DG) showed better performance on binding compared to the control participants. Two patients showed selective temporal order memory impairment (PM and PS), and two showed impaired performance on both spatial and temporal order memory (HB and JB), but not on binding. None of the patients performed significantly below the control mean for the binding condition.

To relate spatial and temporal order memory to traditional neuropsychological task performance, table 3 shows patterns of deficits on standard measures of memory and

Table 3 Performance for the seven individual patients who showed abnormal scores against the normative sample of control participants

					object relocation			neuropsychological assessment[a]						
					spatial	temp-oral	binding	verbal memory			working memory		EF	IQ
patient	**sex**	**edu**	**side[b]**	**age**	**error %**	**error %**	**error %**	**direct recall**	**delay recall**	**recog-nition**	**verbal**	**visuo-spatial**		
MS	f	5	R	25	**46***	29	75	×	✓	✓	×	×	✓	×
DG	m	7	R	50	**42***	8	**0***	×	×	×	✓	✓	✓	✓
LS	m	5	B	60	**80****	29	56	✓	×	✓	✓	✓	✓	✓
PM	m	4	L	65	17	**67***	92	×	✓	×	×	✓	×	✓
PS	m	6	L	75	30	**63***	75	×	×	×	×	✓	✓	✓
HB	f	6	L	67	**67****	**71***	92	×	×	×	-	✓	×	✓
JB	m	5	L	78	**63***	**63***	100	✓	✓	×	✓	✓	×	✓
			control mean	55	15	17	65							
			(SD)	*(17)*	*(13)*	*(17)*	*(27)*							

Note. Abnormality of scores expressed in the (two-tailed) probability that the case's score is an observation from the control population. Higher scores indicate worse performance (% incorrectly replaced objects). a) ✓ indicates no abnormal performance on this task, x a score below the 5th percentile or equivalent standardized score based on existing normative data. **–** indicates a missing data point. The neuropsychological assessment included measures of verbal learning and memory ((D)AVLT direct recall, delayed recall and delayed recognition), verbal working memory (WAIS CLN), visuospatial working memory (Corsi Block), attention/executive functioning (EF, Trail Making A/B index) and abstract reasoning (IQ, Raven Advanced Progressive Matrices short form). b) L = left hemispheric stroke, R = right hemispheric stroke, B = bilateral stroke. *$p < .05$, **$p < .001$, uncorrected

executive functioning. Only one out of the five patients with impairment in spatial location memory showed decreased performance on a standard measure of visuospatial working memory. Decreased performance on the same measure was not found in any of the patients with temporal order memory deficits. In all patients with temporal order memory deficits, one or more aspects of standard measures of verbal (working) memory fell below normal performance, but which specific aspects were affected varied greatly. For example, in one patient (PS) all measures of verbal (working) memory were impaired, in another patient who showed deficits in both spatial and temporal order memory only one standard memory test value fell below normal performance (JB, decreased performance on verbal memory delayed recognition). All patients with spatial location memory deficits also showed decreased performance on at least one measure of verbal (working) memory.

Decreased performance on a measure of attention/executive functioning did not occur in patients with selective spatial location memory deficits, but did occur in one patient with a selective problem in temporal order memory (PM) and in two patients with spatial as well as temporal order memory deficits (HB and JB). Only one of the seven patients showed problems in abstract reasoning, in this patient (MS) only spatial location memory was affected.

Additional data exploration

Lesion localization

In addition to the group analyses, individual patterns also showed laterality effects. Temporal order memory was associated with left lateralization: all four patients with abnormal scores on this measure had left hemispheric strokes. This group represents 25% of the patients with left hemispheric strokes in our sample. In comparison, none of the patients with right hemispheric strokes showed temporal order memory problems. Lateralization of spatial memory was less pronounced. Two out of three patients with selective spatial location memory problems had right lateralized lesions, and one bilateral. The patients who showed both spatial and temporal order memory problems were left hemispheric stroke patients.

It was explored whether lesions in the stroke patients with problems in spatial and/or temporal order memory extended to the frontal, temporal and parietal lobes. Only one of these patients showed damage in the parietal lobe, and this patient displayed problems only with temporal order memory, and not with spatial location memory. To compare, twelve out of the 36 stroke patients (33%) did have parietal lesions, but did not perform abnormally. In two out of the four patients with temporal order memory

deficits, the temporal lobe was affected. The frontal lobe was affected in one patient with selective temporal order memory deficits (PS), and in two of the patients with selective spatial location memory problems (MS and LS).

Discussion

The aim of this study was to investigate functional dissociations between different dimensions of contextual memory in stroke patients, specifically comparing performance on temporal order memory, spatial location memory and binding of temporal and spatial features. These processes are crucial for everyday activities such as navigation, where one needs to both keep track of the location of landmarks along the route as well as the order in which one encounters these. Pinpointing whether spatial and temporal memory processes can be differentially affected by stroke helps to better understand memory problems in patients.

The main outcome of the study was that functional dissociations between spatial and temporal order memory were found, and these were confirmed by lateralization effects.

First, a group effect was observed for temporal order memory, where patients with left-hemispheric lesions showed worse performance than control participants and bilateral stroke patients. Other studies also indicated left hemisphere involvement in temporal order memory (Jacques, Rubin, LaBar & Cabeza, 2008; Hirose et al., 2013). In an extensive review, Nicholls (1996) described a left hemisphere advantage for temporal processes, among which memory for temporal sequences. The left hemisphere is specialized in a specific form of sequential processing: language (where processing of the sequential order of words in a sentence is necessary to distill its meaning). Nicholls states that language is one example of multiple functions of a left hemispheric 'rapid sequential processor' in a broader sense. The current finding that patients with damage in the left hemisphere show impaired performance on the temporal order memory task is in line with this idea, especially since a visual task was used that required little linguistic processing.

No obvious laterality effect was found for spatial location memory on group level. This is slightly surprising, since spatial memory typically shows a right hemisphere bias. One possible explanation could be that when the right hemisphere is damaged, the left hemisphere might be recruited to solve the spatial location task. A verbal encoding strategy might have been applied, since nameable objects were used in the current paradigm (see also Dent & Smyth, 2005; Kessels et al., 2002). Also, the spatial task used

here may be considered to involve categorical spatial relations, and no absolute spatial coordinates (i.e. the spatial locations were predefined and relocation could be solved by labeling of the relative position such as 'the ball was shown *below* the church'). Both verbalization and categorical memory for spatial locations are shown to be preferentially processed in the left hemisphere (Van Asselen, Kessels, Kappelle & Postma, 2008; Van der Ham et al, 2012). This might explain why cerebral asymmetry for spatial location memory was not apparent on group level, and also the finding that some left hemisphere stroke patients fail on both temporal order and spatial location memory. Verbal comprehension problems are not likely to explain the difficulty that left hemispheric stroke patients show on this particular task, as they show no floor effect and were well capable of performing other (sub)tasks with similar instruction difficulty.

Notably, no group differences were observed for binding of temporal order and spatial location memory. Memory problems in different clinical populations do concern binding of different features (Postma et al., 2006; Kessels and Kopelman, 2012). Postma et al. (2006) showed that Korsakoff patients display problems not merely in remembering contextual features separately, but particularly in binding spatial location and temporal order in memory: performance compared to control participants dropped significantly when both features needed to be remembered at the same time. A possible reason for the absence of group effects for binding in the current data is that performance on this test was also low in control participants and yielded high variances. Whether binding problems exist in stroke patients therefore remains inconclusive. However, it does become apparent that stroke patients show single-feature memory deficits, which is also in line with the work of Van Geldorp et al. (2013).

Analysis at individual level further confirmed the presence of dissociations between spatial and temporal order memory. Impairment on temporal order memory was not necessarily accompanied by impairment on spatial location memory. In total, seven (18%) of the included stroke patients showed significantly lower performance on spatial and/or temporal order memory compared to control participants, corrected for age. No binding problems became apparent.

The object relocation tasks were shown to be suitable for patient populations, as well as for elderly people. For example, they did not require computer skills. Also, although scores were not normally distributed, no floor or ceiling effects were found. This is important, since tests that measure specific subcomponents of contextual memory are scarce. Moreover, the current results show that standard neuropsychological assessment falls short in predicting what problems in spatial location and/or temporal order memory may occur in (stroke) patients. Performance on well-known and commonly

used tasks (of memory, executive functioning and abstract reasoning) was overall diminished in the patient group, but is insufficient for providing any reliable indication of what contextual memory aspects may be impaired in patients. Van Geldorp et al. (2013) reached the same conclusion.

Possibly, the currently used paradigm can be applied as diagnostic instrument in clinical neuropsychological practice in the future. Using test material that is sensitive to subtle deficits in these specific functions can be valuable for diagnostic purposes, and can provide insights for patient-tailored cognitive rehabilitation and for development of programs aimed specifically at remembering the location and order in which events occur. To be able to implement the findings in this study to clinical practice, suitability of the application of the paradigm should be tested using additional internal and external validity and reliability analyses, including sensitivity/specificity analyses. Possibly, adaptions should be made in the operationalization of binding, as the test materials at hand showed little discriminability for binding problems in the current sample.

A limitation of the current study is that it was not possible to thoroughly examine the neuro-anatomical underpinnings of the behavioral patterns of functioning that were found. Image acquisition was part of standard clinical care and not standardized. This also limited the available information on stroke severity in the patient sample. Also, between group differences might have been influenced by differences in baseline characteristics. Specifically, the lack of gender matching was a weakness, however, gender was shown not to influence the results. Also, comorbidities and stroke-related confounding factors such as neglect and hemianopia were not formally assessed. However, it is unlikely that these factors could explain the results.

A tentative exploration of the available imaging data indicated a laterality effect, but no conclusive information on the specific involvement of parietal, temporal and frontal brain regions. No clear indication was observed for frontal involvement in temporal order memory or parietal involvement in spatial location memory. It is interesting that none of the patients who suffered problems on spatial location memory showed damage in the parietal lobe (and vice versa), an area commonly associated with (spatial) working memory (Constantinidis & Wang, 2004; Friedman & Goldman-Rakic, 1994; Glabus et al., 2003; Inoue et al., 2004; Zhang, 2004) and that those who showed both spatial and temporal order memory deficits showed unilateral left hemisphere damage. Future studies might focus particularly on the underlying neuro-anatomical architecture, to allow for meaningful interpretation of these observations. Specifically, characteristics of left hemispheric contributions to temporal order memory ask for in-depth investigation.

To summarize: co-occurrence of deficits in spatial location and temporal order memory is not obligatory. These results imply that those types of memory processes are separable. They support the notion that spatial location and temporal order contain functionally separable processing mechanisms. A possible explanation for the co-existence of dissociations and strong associations between processing spatial and temporal order memory might be that memory systems can adapt their function to the task at hand. This is congruent with the ideas of Logie, Brockmole, and Jaswal (2011), who state that the visual working memory system is flexible in allowing formation of bindings between task-relevant features, in the face of major changes in task-irrelevant object properties. The existence of 'hybrid' cells in addition to dedicated cells that react only to spatial or temporal information also shows the flexibility of the underlying neural systems (Howard & Eichenbaum, 2014), and indicates functional plasticity. In this way, the interaction between spatial and temporal aspects of memory is functionally adaptive in the human brain. The results of this study add to our understanding of how contextual information is processed in human memory.

Declaration of interest

All authors declare no conflicts of interest.

Supplementary Material

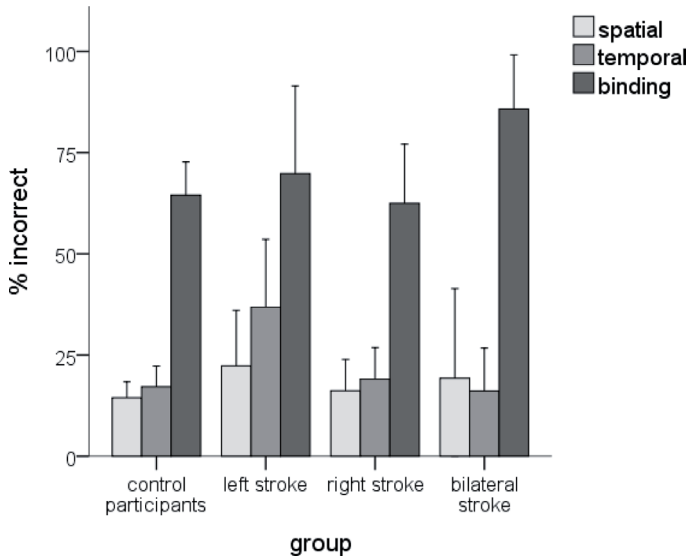

Figure A. *Performance on spatial and temporal order memory and binding, across groups that differ by lateralization of brain damage after stroke. Error bars display the 95% confidence interval.*

Table A Case statistics for the seven individual patients who showed abnormal scores against the normative sample of control participants

	object relocation performance											
	spatial				**temporal**				**binding**			
patient	**error %**	**z-score**	***p***	**z-ccc**	**error %**	**z-score**	***p***	**z-ccc**	**error %**	**z-score**	***p***	**z-ccc**
MS	**46***	2.454	.003	3.407	29	0.696	.128	1.645	75	0.390	.161	1.512
DG	**42***	2.117	.023	2.424	8	-0.519	.682	-0.422	**0***	-2.391	.016	-2.583
LS	**80****	5.061	.001	5.364	29	0.696	.536	0.639	56	-0.314	.610	-0.526
PM	17	0.197	.981	-0.025	**67***	2.902	.006	2.944	92	1.020	.415	0.846
PS	30	1.170	.457	0.780	**63***	2.666	.026	2.395	75	0.835	.787	0.282
HB	**67****	4.088	.001	4.137	**71***	3.166	.004	3.180	92	1.020	.455	0.776
JB	**63***	3.738	.002	3.486	**63***	2.666	.033	2.309	100	1.317	.485	0.736
control	15				17				65			
m*(sd)*	*(13)*				*(17)*				*(27)*			

Note. Abnormality of scores expressed in z-values and (two-tailed) probability that the case's score is an observation from the control population, with effect sizes (z-ccc). Higher scores indicate worse performance (% incorrectly replaced objects). *$p < .05$, **$p < .001$, uncorrected

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6

Cognitive Correlates of Time Perception: a Neuropsychological Patient Study

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Abstract

Introduction: Time perception in the supra-second range is thought to be mediated by cognitive processes. We investigated whether different aspects of time perception (estimation, reproduction and production of time intervals) could be dissociated, and to which cognitive functions they relate.

Method: A direct comparison between clock speed and variability on different dimensions of time perception (estimation, reproduction and production) was made, and correlations with neuropsychological tasks for (working) memory, executive functioning and processing speed were investigated in 37 stroke patients, compared with 38 healthy age- and education-matched control participants.

Results: Seven stroke patients (19%) showed deficits in time perception. Selective impairments occurred on time estimation and reproduction subtasks. Time estimation and reproduction variability were significantly correlated with measures of working memory and information processing speed.

Discussion: Estimation and reproduction of time intervals were shown to be dissociable. Moreover, the results concur with time perception models that incorporate the integration of supra-second timing and other cognitive processes, through interactions between subcortical and cortical brain regions.

Introduction

The perception of passage of time is variable and context dependent. Some moments seem to fly by, while others don't ever seem to end. Also, individual differences in the subjective experience of time can be observed. Where Toto sings that 'time passes quickly' in the song "Stop loving you", Bob Dylan states that "Time passes slowly". Pathological deviances in time perception can lead to serious problems in daily life participation. For example, one of our stroke patients experienced trouble planning his daily schedule, as he tended to arrive far too early for his appointments. It turned out that he overestimated the duration of travelling from his apartment to the therapists' office. Fortunately, after providing feedback by timing his travels with a stopwatch, this patient was able to adjust.

Several researchers have tried to pinpoint how the brain processes time duration, and what causes individual differences in their perception of time duration. There is no dedicated sensory system for time processing (Ivry & Schlerf, 2008). Instead, sense of time has to be derived from other signals. One burning question is whether there is a specific, context-independent and supramodal 'brain clock' (Gibbon, Church, & Meck, 1984), or whether time perception is integrated in different 'state dependent' temporal processors in functionally distributed specialized areas of the brain (Fontes et al., 2016; Ivry & Schlerf, 2008). The intrinsic models are based on either the time course of neuronal firing ('process-decay' models), or concurrent patterns of neural activation: oscillator/coincidence-detection models. The latter follow from the idea that (the onset of) a temporal stimulus generates synchronized neural activity (oscillations), which signals certain mechanisms that are sensitive to these coincident patterns of activation (Ivry & Schlerf, 2008).

Brain areas that have been identified as important for time processing are the cerebellum, basal ganglia and (frontal) cortex (Meck, 2005), with different mechanisms involved in interval ranges under a second (sub-second) compared to durations longer than one second (supra-second). Cerebellar lesions in particular affect implicit timing of sub-second durations (Meck, 2005). The basal ganglia seem involved in explicit timing (requiring an overt response (Shih, Kuo, Yeh, Tzeng, & Hsieh, 2009) in both the sub-second and seconds range (Coull, Cheng, & Meck, 2011), and may have a role in determining the speed of the internal clock as a centralized, context-independent, supra-modal timer. For supra-second time processing, the basal ganglia interact with cortical regions such as the supplementary motor area and the prefrontal cortex (Teixeira et al., 2013)) to form a functionally integrated corticostriatal network (Coull et al., 2011; Matell & Meck, 2000; Teixeira et al., 2013). The underlying mechanism is thought

to reflect the oscillator/coincidence-detection model, as the striatum is thought to detect coincident activity of cortical neurons, which are synchronized by the onset of a stimulus. This model seems biologically feasible and is validated by animal lesion and pharmacological studies, showing an important role of the dopaminergic system and the basal ganglia in clock speed, and of cholinergic pathways and the (frontal) cortex in the integration of timing and memory (Coull et al., 2011; Fontes et al., 2016; Teixeira et al., 2013).

Differences appear to exist in the extent to which cognitive processes are involved in sub-second versus supra-second time processing. Shorter durations may be processed relatively automatic and are more directly connected to elementary sensory mechanisms. Longer intervals seem more modality independent (Ivry & Schlerf, 2008) and cognitively driven (Coull, Cheng, & Meck, 2011). Processing of time intervals in the supra-second range has been claimed to relate to several cognitive functions. Most theories distinguish three different functional components: 1. a clock component, which' speed is modifiable, amongst others by attentional processes, 2. the memory component, that stores clock output values, and 3. a decision/comparison component that is used to compare the current clock value to previously stored duration memories (Matell & Meck, 2000; Morillon, Kell, & Giraud, 2009). Errors are often attributed to limited attentional and working memory capacity. Block, Zakay, and Hancock (1998) found that experienced duration lengthens as a function of the amount of attentional resources allocated to processing the passage of time. The amount of pulses being processed is thought to be mediated by an 'attentional gate'. The more attention is recruited for competing non-temporal tasks, the fewer resources are left for temporal processing, the fewer pulses are counted and the shorter the perceived duration (in estimation tasks). Distractions during processing of passage of time lead to greater errors in perception. Overestimation and underproduction can occur in experimental settings, where a disproportionate large amount of residual resources is available, as opposed to natural situations where many nontemporal stimuli compete for attention with time processing tasks.

Reproduction can also be distorted by memory problems, as one must remember the target duration at the time of reproduction (Mioni, Mattalia, & Stablum, 2013) and by problems in executive functions such as switching (Ogden, Wearden, & Montgomery, 2014), updating (Ogden, Salominaite, Jones, Fisk, & Montgomery, 2011), monitoring (Vallesi, McIntosh, Shallice, & Stuss, 2009), and comparison with a memorized standard (Rao, Mayer, & Harrington, 2001).

The idea that attention, (working) memory and executive functioning are important for time perception has been used to explain age-related differences in children (Zélanti & Droit-Volet, 2012) and in elderly (Baudouin, Vanneste, Isingrini, & Pouthas, 2006; Block et al., 1998), as well as problematic time perception in clinical populations, such as ADHD (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001), TBI (Mioni et al., 2013; Perbal, Couillet, Azouvi, & Pouthas, 2003) and Alzheimer's disease (Elhaj, 2014).

With respect to supra-second time perception in stroke patients, mixed results have been found. In 1997, Rubia, Schuri, von Cramon, and Poeppel reported an investigation of persons with right or left middle cerebral artery infarcts on time estimation and production tasks. They found that patients with right as well as patients with left hemisphere infarcts were inaccurate. The patterns of performance differed, however, in that patients with right hemisphere lesions behaved as if the clock was running too fast, whereas those with left hemisphere lesions did not demonstrate a consistent effect on "clock speed". Danckert et al. (2007) also reported patients with right hemisphere lesions to underestimate durations. Other authors only observed clock speed errors in patients with cerebellar lesions, whereas patients with (pre)frontal lesions showed mostly indirect timing deficits related to attention and working memory (Casini & Ivry, 1999; Mangels, Ivry, & Shimizu, 1998). Kagerer, Wittmann, Szelag, and Steinbüchel (2002) reported timing deficits only for longer durations following right prefrontal damage. Coslett, Shenton, Dyer, and Wiener (2009) demonstrated that stroke patients' performance was consistent with a "fast clock". They under-produced but overestimated time intervals varying from 4-12 seconds, whereas they performed relatively well on reproduction. Lesion overlap analysis showed possible involvement of the parietal lobe, but no laterality effects. Coslett et al. conclude that multiple structures and different cognitive functions may be involved.

To our knowledge, a direct comparison of the different cognitive functions that are involved in time estimation, reproduction and production in a single study with a clinical population has not been performed before. Ergo, the aim of the current study was to investigate possible functional dissociations between different dimensions of time perception (time estimation, reproduction and production) in neurological patients, as well as the related cognitive processes in each of these aspects of time perception. This was studied in patients with focal cerebral lesions, caused by stroke. These patients comprise an ideal population to study dissociations in cognitive processes because of their heterogeneity in terms of brain lesion localization, which allows for broad exploration. We investigated whether different aspects of time perception could be related to different cognitive functions. Where time estimation and production performance would mainly depend on the internal clock rate (mediated by attentional resources),

reproduction could be expected to rely more heavily on cognitive processes (memory, executive functioning) underlying temporal processes, rather than on internal clock speed (Mioni et al., 2013).

Method

Participants

From the University Medical Center Utrecht (UMCU) 37 patients were recruited with a diagnosis of stroke based on clinical assessment and confirmed by imaging of the brain (CT, MRI), in accordance with inclusion regulations described in UMCU Medical Ethical Committee protocol 05-109. The patients were selected from a database of patients who participated in a larger study on cognitive functioning after stroke. Part of this extended study has been reported elsewhere (Kant et al., 2014). Exclusion criteria were comorbid psychiatric or neurological diseases and conditions (such as diagnosis of dementia, as derived from the medical charts of the patients) and pre-existing impairments that would limit completion of the assessment (such as blindness). Practice conditions of the experimental procedure were used to screen whether there were any confounding (stroke-related) factors that would hamper task performance.

Indications of stroke severity in terms of impact on activities in daily living (ADL) were derived from medical status at time of discharge. Barthel Index (Mahoney & Barthel, 1965) scores were estimated for each patient.

Location of lesion was confirmed by an experienced neurologist (CJMF), using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans that were obtained according to clinical practice. All available scans were used to determine the ultimate structural damage as exactly as possible, using a human brain atlas as reference (Duvernoy, 1999).

Thirty-eight age- and education-matched people without self-reported neurological or psychiatric disorders served as control participants. These participants were either spouses or family of patients or volunteers who came to our attention through word of mouth. Participants were treated in accordance with the Declaration of Helsinki.

Educational level was coded according to Verhage and Van der Werff (1983), range 1 through 7 from less than primary school to university degree. Intelligence (premorbid) was estimated using the Dutch version of the National Adult Reading Test, scores cor-

rected for age and gender (Schmand, Bakker, Saan, & Louman, 1991). Dexterity was assessed using the Annett Handedness Inventory (Annett, 2004).

Materials

Time perception

To investigate dissociations between different aspects of time perception, a similar paradigm was used to that of Coslett et al. (2009). Three variants of time perception (time estimation, time reproduction and time production) were operationalized in the auditory modality using a dual-task paradigm. Performance was measured by accuracy of estimation, reproduction and production of tones with different durations (2-20 seconds, adapted from Barkley et al. (2001), all believed to fall within the time span of working memory (Baddeley, 1992; Mimura, Kinsbourne, & O'Connor, 2000). A control task was administered to prevent overt counting strategies.

Stimuli were created with E-prime™ software (PST Tools®) and were administered on a computer with a 17" inch LCD screen (viewing distance = 65cm, 1024x768 resolution). All auditory stimuli took the form of a three note C-E-G chord with C at a frequency of 261.63 Hz (C4). Sound was played through a standard set of computer speakers at a fixed volume for all participants. Responses were collected with a custom-made response box, as an extension of the original E-prime™ Response Box (PST Tools®). It had two large identical buttons of different color; one red, one green.

Durations were 2, 5, 8, 12, 15 and 20 seconds. Each stimulus was administered twice, creating a total of 12 trials per task. Each trial block was preceded by a practice trial with duration of 9 seconds.

To minimize the effect of (sub-vocal) counting strategies, a secondary task had to be performed in parallel with each time perception task. During presentation of each stimulus, participants were instructed to pay attention to a colored rectangle (3.8 x 4.0 cm, or 138 x 143 pixels) in the center of the screen. At pseudo-random intervals, the color of this rectangle would change, at which point the subject was instructed to verbally report on the new color. There were four possible colors (red, blue, green and yellow) and six possible intervals (1500, 1700, 1900, 2100, 2300 and 2500 milliseconds). Participants were instructed that the accompanying time perception task should be given the highest priority.

Subjects advanced through each task by pressing the green button on the response box and could (re)produce intervals by pressing and holding the red button. While

holding the button, the C-chord was played through the speakers. There were no time limitations in the response phase and trial-by-trial progress was always self-paced.

In the first condition (time estimation), participants were asked to estimate the length of auditory stimuli ("tones") presented to them, in seconds. Their response was recorded on a scoring sheet. In the second condition (time reproduction), participants were asked to replicate the duration of a sample tone. After presentation of the stimulus, participants had to press and hold a response box button to replicate the sample tone. Both during presentation of the sample tone and reproduction, the secondary task had to be performed in parallel. In the third condition (time production), participants were asked to create tones with specified lengths by pressing and holding the red button on the response box, after the instructed duration in seconds was presented on the screen. The order of administration was always the same, to minimize and standardize the effect of prior knowledge on subsequent conditions (e.g. if the production condition would precede the estimation condition, the participant would already know what interval lengths were used).

Cognition

Standardized neuropsychological tasks were included that measured (working) memory, speed of information processing and attention/executive functioning. The Dutch version of the Rey Auditory Verbal Learning Test (Saan R.J. & Deelman, 1986) was administered to measure verbal learning, delayed recall and recognition memory. To assess verbal working memory, the Letter Number Sequencing task was used (a subtest of the Wechsler Adult Intelligence Scale III, Wechsler, 1997). Visuospatial working memory was measured with the Corsi-Block task (Kessels, Roy P. C., Martine J. E. van Zandvoort, Albert Postma, L. Jaap Kappelle, 2000). Speed of information processing and attention/executive functioning were measured by the Trail Making Test parts A and B (Reitan & Wolfson, 1992).

Data analysis

Outcome measures

Outcome measures per condition were the mean (relative) absolute and signed errors over the 12 experimental trials, in seconds. The absolute error represents variability or accuracy of the responses, the signed error represents the 'clock speed': systematic over- or underestimation and/or (re)production (Gunstad, Cohen, Paul, Luyster, & Gordon, 2006). Larger deviances are expected with longer durations (Barkley et al., 2001; Matell & Meck, 2000). Therefore, the relative error was calculated, by dividing the deviation for each trial by its duration.

General differences

To check for adequate matching of demographical variables and explore differential neuropsychological task performance between patients and control participants, group differences were tested using chi-square tests (gender, dexterity), Mann-Whitney U (educational level), two-tailed independent t-tests (age, IQ) and univariate analyses of (co)variances, controlling for gender (cognitive variables).

Dissociations in time perception

A repeated measures 2x3 design was used, with one between group factor (control participants versus stroke patients) and one within group factor: time perception task condition (time estimation, reproduction and production). Separate analyses were performed for each error type (variability and clock speed). Gender was added as covariate.

Individual patterns

Because of heterogeneity of the patient group in terms of lesion location, a case study approach was used to investigate individual patterns of performance and dissociations with respect to lesion location. Statistical procedures by Crawford were applied (Crawford, Garthwaite, & Ryan, 2011; Crawford & Howell, 1998). Using these methods, single test scores were compared with norms derived from the control sample, to make an appropriate parametric statistical analysis of possible deficits. Essentially, this method is a modified independent samples t-test in which the individual is treated as a sample of N = 1. For the current study, the program "BTD_cov" was used: the Bayesian test for a deficit in a single case controlling for covariates, as described by Crawford et al. (2011) Abnormalities of patients' scores were tested, correcting for age.

In addition to the investigation of functional dissociations, observed patterns of lesion localization were explored to search for indications whether the results are congruent with existing theories on the underlying neuroanatomy.

Cognitive correlates of time perception

Correlations between time perception conditions and cognitive variables measuring (working) memory, speed of information processing and attention/executive functioning were investigated.

Results

Demographical data and patient characteristics

Table 1 shows that control participants did not differ from the patients with respect to level of education, (premorbid) intelligence, dexterity, and age, but the ratio females was higher than in the stroke patients. Stroke is more prevalent in males (Wilson, 2013), and control participants typically included spouses and family members from the opposite sex, resulting in the unbalanced matching on this aspect. Potential influence of gender was therefore examined. No significant gender differences on any of the time perception measures were found using individual t-tests ($p > .05$). Following a conservative approach, gender was nevertheless added as covariate in subsequent group analyses.

Table 1 Patient and Control Participant Demographics

Variable	Patients *N = 37*	Control participants *N = 38*	Significance *p*	Effect size
Age (M ± SD)	58 ± 14	55 ± 16	.366	$r = .010$
Gender (% male)	70 %	45 %	.025*	$\varphi = -.258$
Dexterity (% righthanded)	79 %	70 %	.638	$\varphi = .055$
Educational level (median (IQR))	5 (1)	6 (1)	.584	$r = -.063$
IQ (M ± SD)	108 ± 18	109 ± 14	.745	$r = -.038$

Note. Group differences between patients and control participants were tested using chi-square tests (gender, dexterity), Mann-Whitney U (educational level) and two-tailed independent t-tests (age, IQ). $*p < .05$

In the patient group, ischaemic strokes predominated (16% haemorrhagic). Average interval between date of stroke and testing was 17 months (SD = 8.2). Time between the index event and scanning varied, with a median of 4 days (interquartile range 1-16.5, when no infarction was visible on day 0 follow-up scans were used to confirm location of lesion). No influence of elapsed time between event and test date or between event and date of most recent scan was found on any variable. For 10 patients, only CT scans were available. Lesion locations in patients were widespread throughout the brain; 16 patients had strokes in the right hemisphere, 13 in the left, and 8 showed bilateral damage. Two patients had a history of a previous stroke.

For 21 out of the 37 patients (57%), no significant ADL limitations were reported as they scored 20/20 on the Barthel index. The remaining 16 patients (43%) were mildly dependent in functional ability at time of discharge (Barthel index score range 15-19). Mean stay on the neurology unit was 13 days (SD = 14). Destination of discharge was

unknown for 1 patient, home for 57% of the patients (n = 21), 10 patients (27%) were sent to a rehabilitation centre, and 5 patients (14%) were admitted elsewhere (to a hospital or residential care facility). Duration of hospital admission and estimated stroke severity (as indicated by Barthel Index scores) were not significantly correlated to the experimental variables, and there was no significant effect of discharge destination on the experimental variables either ($p > .05$).

General group differences

Table 2 shows that patients on average scored worse than control participants on verbal working memory/attention, information processing speed and memory learning and recognition.

Table 2 Group differences between stroke patients and control participants on cognitive variables

Variable	Patients *N = 37*	Control participants *N = 38*	Significance *p*	Effect size η_p^2
Verbal working memory/attention	8.7 (3.6)	11.6 (2.9)	<.001*	.188
Visuospatial working memory/ attention forward	7.7 (1.5)	8.1 (1.8)	.176	.026
Visuospatial working memory/ attention backward	7.5 (2.0)	8.7 (2.1)	.006	.101
Information processing speed	47.2 (23.7)	32.6 (13.5)	.003*	.116
Executive functioning/switching	2.4 (1.1)	2.1 (0.6)	.235	.020
Memory learning	40.8 (13.8)	52.1 (10.1)	<.001*	.157
Memory recall	8.7 (4.0)	11.3 (3.0)	.011	.087
Memory recognition	27.5 (3.7)	29.6 (0.9)	.005*	.107

Note. Group differences between patients and control participants were tested using univariate analyses of variances, controlling for gender. Higher scores represent better performance for the verbal and visuospatial working memory/attention and memory tasks. Higher scores represent worse performance for information processing speed and executive functioning/switching. *$p < .006$, Bonferroni corrected for multiple comparisons.

Group analyses of time perception measures

Repeated measures analyses of (co)variance were performed using a 2x3 design with group as between-subjects factor (patients versus control participants), time perception condition as within-subjects factor (time estimation, reproduction and production) and gender as covariate. Separate analyses were performed for both error types: variability and clock speed.

Variability

Mauchly's test indicated that the assumption of sphericity was violated for the main effect of condition. Therefore, the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε = .73).

A significant main group effect was found, F (1, 72) = 5.48, p = .022. Effect size η_p^2 = .071, observed Power = .636, indicating overall lower performance for the patient group. No significant main effects were found for gender, condition, or the interaction between group and condition (p > .05).

Post-hoc univariate analyses of (co)variance did not show significant effects on group level for the three conditions (estimation, reproduction and production) separately (see table 3, p > .05).

Table 3 Time perception task performance

Variable	Patients *N = 37*	Control participants *N* = 38	Significance *p*	Effect size η_p^2
Time estimation variability	0.53 (0.64)	0.41 (0.46)	.149	.029
Time estimation clock speed	0.09 (0.73)	0.10 (0.54)	.597	.004
Time reproduction variability	0.32 (0.24)	0.25 (0.09)	.120	.033
Time reproduction clock speed	-0.06 (0.26)	-0.17 (0.12)	.177	.025
Time production variability	0.49 (0.45)	0.33 (0.19)	.075	.043
Time production clock speed	0.30 (0.58)	0.03 (0.35)	.081	.042

Note. Group differences between patients and control participants were tested using univariate analyses of variances, controlling for gender. Higher scores represent worse performance for time variability measures. For clock speed, negative values represent underestimation/(re)production, and positive values overestimation/(re) production.

Clock speed

Mauchly's test indicated that the assumption of sphericity was violated for the main effect of condition. Therefore, the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity (ε = .68).

A significant main group effect was found, F (1, 72) = 4.63, p = .035. Effect size η_p^2 = .060, observed Power = .565. Also, there was a significant effect of condition (F (1.37) = 7.39, p = .004, effect size η_p^2 = .093, observed Power = .852. Pairwise comparisons showed significantly lower values of time reproduction (mean = -0.10 (SE 0.02)) compared to time estimation (mean = 0.09 (0.07), p = .03) and time production (mean = 0.16 (0.05), p < .001), and no significant difference between time estimation and production (p > .05). Participants overall reproduced shorter intervals with respect to sample durations, whilst they overproduced intervals with a pre-specified duration and tended to overestimate the duration of sample intervals.

No significant main effects were found for gender or the interaction between group and condition (see table 3, p > .05).

Post-hoc univariate analyses of (co)variance did not show significant effects on group level for the three conditions separately (see table 3, p > .05).

The assumption of independence was violated, as the residuals were not normally distributed for all variables.

All participants were able to perform the tasks according to procedure without difficulty in using the computerized response box and could adequately process stimuli without apparent auditory, visual or attentional problems.

Individual patterns

Seven individual patients (19 %) displayed time perception difficulties (see tables 4 and 5). Two patients were selectively impaired on time estimation, two other patients solely on time reproduction. Three patients showed concurrent deficits in reproduction and production. Errors in estimation and production were never systematic underestimation or -production, but mostly overestimation and -production.

Table 4 Case statistics for the seven individual patients who showed abnormal scores against the normative sample of control participants on time perception variability

				time perception variability								
				estimation			**reproduction**			**production**		
patient	**sex**	**side**	**age**	**error**	***p***	**z-ccc**	**error**	***p***	**z-ccc**	**error**	***p***	**z-ccc**
AC	f	R	36	3.92	**< .001***	8.589	0.17	.542	-0.643	0.20	.628	-0.512
MP	f	R	47	1.53	**.010***	2.786	0.43	.043	2.163	0.39	.703	0.395
JB	m	L	78	0.22	.360	-0.978	0.52	**.013***	2.751	0.20	.394	-0.910
JQ	f	L	79	0.57	.859	-0.189	0.53	**.011***	2.851	0.29	.680	-0.441
PM	m	L	65	0.46	.910	-0.117	1.55	**< .001***	14.666	1.20	**< .001***	4.537
PS	m	L	75	0.43	.691	-0.421	0.66	**< .001***	4.388	2.61	**< .001***	11.948
HW	m	R	73	0.31	.536	-0.652	0.26	.894	-0.140	1.33	**< .001***	5.153
		control mean		0.41			0.25			0.33		
		(SD)		*(0.46)*			*(0.09)*			*(0.19)*		

Note. Abnormality of scores expressed in the (two-tailed) probability that the case's score is an observation from the control population, with effect sizes (z-ccc). Higher scores indicate worse performance. L = left hemispheric stroke, R = right hemispheric stroke, B = bilateral stroke. *$p < .017$, Bonferroni corrected for multiple comparisons.

Table 5 Case statistics for the seven individual patients who showed abnormal scores against the normative sample of control participants on time perception clock speed

				time perception clock speed								
				estimation			**reproduction**			**production**		
patient	**sex**	**side**	**age**	**error**	***p***	**z-ccc**	**error**	***p***	**z-ccc**	**error**	***p***	**z-ccc**
AC	f	R	36	3.62	**< .001***		-0.04	.292		-0.17	.550	
MP	f	R	47	1.10	.063		0.16	**.011***		-0.39	.242	
JB	m	L	78	0.15	.874		0.10	.043		0.09	.818	
JQ	f	L	79	-0.57	.155		-0.07	.460		0.00	.992	
PM	m	L	65	-0.46	.265		1.09	**< .001***		1.20	**.002***	
PS	m	L	75	-0.43	.250		-0.66	**< .001***		2.60	**< .001***	
HW	m	R	73	-0.31	.355		0.19	**.007***		1.33	**.001***	
		control mean		0.10			-.017			0.03		
		(SD)		*(.054)*			*(0.12)*			*(0.35)*		

Note. Abnormality of scores expressed in the (two-tailed) probability that the case's score is an observation from the control population, with effect sizes (z-ccc). Higher scores indicate worse performance. L = left hemispheric stroke, R = right hemispheric stroke, B = bilateral stroke. *$p < .017$, Bonferroni corrected for multiple comparisons.

Patients with time perception deficits had lesions in both cortical and the subcortical areas (see table 6). No clear pattern could be derived from these data on which brain regions are involved in different conditions (estimation, reproduction and/or production). Affected brain regions include those previously associated with (supra-second)

Table 6 Lesion localization of the stroke patients who displayed time perception deficits

patient	sex	age	side	cortical lesions	subcortical lesions	time perception deficit
AC	f	36	R	parietal, occipital	-	estimation
MP	f	47	R	frontal, temporal, insula	basal ganglia, internal capsule , corona radiata	estimation
JB	m	78	L	temporal	-	reproduction
JQ	f	79	L	frontal, temporal, parietal, insula	basal ganglia, external capsule , corona radiata	reproduction
PM	m	65	L	insula	basal ganglia, internal and external capsule, corona radiata	reproduction/ production
PS	m	75	L	frontal, temporal, parietal, insula	basal ganglia, external capsule , claustrum	reproduction/ production
HW	m	73	R	-	thalamus, internal capsule, corona radiata	reproduction/ production

Note. R = right hemispheric stroke, L = left hemispheric stroke.

time perception such as the basal ganglia and (frontal) cortex, in both the left and right hemisphere. None of these patients displayed cerebellar lesions.

Cognitive correlates of time perception

Distinct dimensions of time perception were correlated to different cognitive variables: time estimation and reproduction variability was significantly correlated with all working memory indices, as well as with speed of information processing (see table 7). In contrast, time production variability and all clock speed measures were not significantly correlated with any cognitive measure.

Table 7 Correlations between time perception and cognitive variables in the total sample (N=75, Spearman's rho)

	Working memory/attention			*Memory*			*Processing*	*Executive*
	Verbal	Visuospatial forward	Visuospatial backward	Learning	Recall	Recognition	*speed*	*functioning/* switching
Time estimation								
variability	**-.396****	**-.421****	**-.459****	**-.308***	**-.311***	-.151	**.342***	.263
clock speed	.017	-.119	-.117	-.151	-.111	.087	-.055	-.016
Time reproduction								
variability	**-.424****	**-.510****	**-.481****	**-.526****	**-.453****	-.237	**.409****	.063
clock speed	-.158	-.013	-.125	-.090	-.044	-.100	.284	.061
Time production								
variability	-.271	-.251	-.218	-.174	-.176	-.204	.237	.059
clock speed	-.078	.082	.148	.004	-.034	-.113	.137	-.004

Note. Bonferroni correction adjusted criterion alpha levels were used: *$p < .008$, **$p < .001$

Discussion

The aim of this study was to investigate functional dissociations between different aspects of time perception in stroke patients, specifically comparing performance on time estimation, reproduction and production, as well as mapping the related cognitive processes to each of these dimensions of time perception.

The outcome of the overall group analyses was that stroke patients and control participants performed differently on time perception in general (with worse performance for patients on variability), although no significant differences were found for each separate condition (estimation, reproduction, production) on group level. There was a significant effect of condition with respect to systematic errors, related to clock speed. Participants overall reproduced shorter intervals with respect to the duration of the sample tones, whereas they overproduced intervals with a pre-specified duration and tended to overestimate the duration of sample tones.

In order to further investigate patterns of dissociation, we subsequently determined which individual patients performed significantly worse on the time perception tasks compared with the control group. The case study analyses showed that seven patients (19 %) displayed obvious time perception difficulties, four of whom were impaired selectively on a single time perception aspect (estimation or reproduction), whereas three showed concurrent deficits in reproduction and production. This demonstrated functional dissociations. Errors in estimation and production are often thought to reflect the same process: changes in clock speed by either limited mental capacity or excessive allocation of attention to the task (Block et al., 1998). If this assumption would hold, deficits in these conditions would always co-occur. The current results contradict this idea.

The results did not show obvious effects of changed clock speed in stroke. This in contrast with previous studies that described stroke patients to display signs of a 'fast clock' (Coslett et al., 2009; Danckert et al., 2007; Rubia et al., 1997). Other authors did not find consistent effects of changed clock speed in stroke (Casini & Ivry, 1999; Kagerer et al., 2002; Mangels et al., 1998). Also, no clear laterality effect was apparent in our sample, and in literature conflicting results are found on that matter as well: some authors do find indications of lateralization (Kagerer et al., 2002; Rubia et al., 1997), others don't (Coslett et al., 2009).

The timing problems that occur in stroke patients may not be easily reduced to a unitary construct, since often multiple cognitive functions are involved. Impaired performance

may reflect the effect of lesions on interactions within complex neural networks. It thus appears that both reduced and increased clock speed can result from strokes in the left and right hemispheres.

Distinct dimensions of time perception turned out to correlate with different cognitive variables: time estimation and reproduction variability were significantly correlated with all working memory indices, as well as with speed of information processing. In contrast, time production variability and all clock speed measures were not significantly correlated with any cognitive measure.

The result that reproduction, but not production, was correlated with working memory, is in congruence with previous findings (Baudouin et al., 2006; Mioni et al., 2013). Baudouin et al. stated that time production would be more dependent on clock speed, and reproduction more on working memory capacity. They found that better working memory scores led to greater accuracy. In contrast to Baudouin et al. (2006), we found no systematic overproduction with fewer working memory/attentional resources. Where they stated that when less attention is allocated to the task, it would require more 'pulses' to reach the target duration, thus elongating the production time, we found no such pattern of results. Perhaps this idea, derived from early models of time processing including a pacemaker that generates pulses and an accumulator that counts these pulses (Gibbon, Church, & Meck, 1984) is too simplistic to account for the complexity of timing behavior.

In the current study, time estimation was also found to correlate with working memory. This is different from Ogden et al. (2014), who found that estimation did not rely on working memory capacity, attention and executive functioning, and time reproduction did. Their explanation was that the cognitive demand for time estimation is lower, as the participants are only processing and maintaining one stimulus at a time. Possibly, the cognitive load of the current paradigm was relatively higher, as a parallel task was added to prevent overt counting (the colour naming).

No correlation was found between aspects of time perception and long term memory recognition. Time perception deficits were previously linked to long term memory dysfunction (Williams, Medwedeff, & Haban, 1989). It seems important for time perception to be able to actively recruit information from long term memory an=d compare previously stored interval durations with the current task in working memory. For even longer durations (i.e. minutes), long term memory recruitment could however be more important than for relatively shorter durations that are still within the working memory range (Mimura, Kinsbourne, & O'Connor, 2000).

Moreover, also no correlation was found between time perception tasks and executive functioning, as measured by a divided attention task. This is surprising, as Ogden et al. (2014) did find time reproduction to be related to attention switching. One could argue that the attentional load in the task was relatively high, since a dual-task paradigm was used, with subjects performing two tasks in parallel: time perception and the counting-suppression task (colour naming).

Information processing speed was also found to be correlated with time processing. Faster information processing speed may contribute to overall cognitive capacity and thereby facilitate time perception performance, especially when nontemporal processes are competing with time perception tasks for cognitive resources, as described in the 'attentional gate' model (Zakay & Block, 1996). Pouthas & Perbal (2004) also found information processing speed to relate to time production (but not to reproduction).

In the present study, patients with time perception deficits showed cortical as well as subcortical damage following stroke, including regions previously associated with supra-second time perception such as the basal ganglia and (frontal) cortex, in both the left and right hemisphere. None of these patients had cerebellar lesions, which supports the discriminant validity of the tasks that were used, as cerebellar damage has been associated merely with sub-second time perception.

These findings are congruent with theories that state that supra-second time perception is processed in interactions between subcortical and cortical brain regions, integrating timing with other cognitive processes.

A limitation of the current study was that neural correlates could not be thoroughly examined, as no standardized image acquisition was performed. The current results do not permit to draw conclusions on what brain regions are involved in different aspects of time perception. Thus, the neuro-anatomical underpinnings of the behavioral patterns of functioning that were found remain object of future investigation. In particular, the contribution of different subcortical (basal ganglia) and cortical (supplementary motor area, prefrontal cortex) brain regions would be relevant for further study on supra-second time perception.

A strongpoint of the study was that time estimation, reproduction and production were investigated in a single study, using the same paradigm, making it possible to directly compare these different dimensions of time perception. In addition, these aspects of time perception were related to multiple cognitive functions, to be able to test assumptions on the functional correlates of time perception. All of the participants were able

to perform the tasks without difficulty. Thus, these tasks were shown to be suitable for use in selected clinical populations.

In sum: functional dissociations were found between time estimation, reproduction and production, as it was shown that these aspects of time perception could be differentially affected in stroke patients. Results further indicate several cognitive functions to be related to time perception: working memory and information processing speed correlated with time estimation and reproduction variability. Together the current results provide further insights in the complex cognitive architecture of time perception.

Declaration of interest

All authors declare no conflicts of interest.

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7

The Cognitive Profile of Advanced Multiple Sclerosis

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Abstract

Background: With progression of multiple sclerosis, neural damage accumulates. However, the consequences for cognitive functioning are mostly studied in relatively early and mild stages of the disease.

Objective: Gain insight in cognitive impairment in advanced MS patients.

Methods: Neuropsychological assessment covering all major cognitive domains, mood, and disease impact, was performed in fourty-four multiple sclerosis patients with severe disabilities to such an extent that they required assisted living. Performance was compared with thirty-five control participants.

Results: A broad range of cognitive functions was affected in the patient group, including those that were previously thought to remain unaffected in multiple sclerosis, such as recognition memory. Deficits in information processing speed were prominent and highly prevalent, and determined cognitive performance in the domains of memory, attention/executive functioning and praxis.

Conclusion: Multiple sclerosis patients in advanced stages of the disease display severe and widespread cognitive deficits, more than and different to those usually described in multiple sclerosis. The cognitive profile in these patients shows a prominent role for reduced information processing speed, affecting performance in all cognitive domains. Thus, data and recommendations from literature biased towards less advanced disease stages are not necessarily applicable to patients with more severe disabilities.

Introduction

Cognitive impairment is prevalent in an estimated 43-65 % of patients with multiple sclerosis (MS) and it is one of the most important factors of the disease to affect daily life participation.[1-3] Cognition in MS has become a growing field of interest for neuroscientists, and research methods have improved significantly.[4] However, patients with progressive MS and severe disabilities are remarkably underrepresented in scientific research and the literature on cognition in this group is inconclusive.

Cognitive deterioration in MS has been considered a form of subcortical dementia or the result of a 'white matter disconnection syndrome'. However, it has been demonstrated that grey matter damage is involved as well.[1, 5] Some argue that, as in relapsing remitting (RR)MS, in progressive MS mostly speed of information processing is impaired,[6] while others report a variety of cognitive functions to be affected in progressive MS.[2, 7-11] The few available comparative studies between primary progressive (PP)MS and secondary progressive (SP)MS led to contradictory findings.[12, 13] Moreover, in studies on cognition in progressive MS, not all cognitive domains were covered in the neuropsychological assessment. This is surprising, because as grey and white matter pathology become more prominent with progression of MS, more severe cognitive deficits may be expected.[14-16]

The present study aimed to provide insight in the nature and severity of cognitive deficits in patients with advanced MS. To this aim, cognition was examined in MS patients with high levels of disability in terms of physical problems and problems in daily functioning, to such an extent that they require assisted living. Secondary analyses were performed to investigate possible confounding effects of mood (depression and anxiety) on cognitive performance. Also, the perceived disease impact was investigated, as cognitive functioning is important in determining the ability to maintain independency in daily life functioning.

Materials and methods

Participants

The MS patients were tested at Nieuw Unicum, center for professional community care and MS expertise center located in Zandvoort, the Netherlands. All MS patients who are admitted to Nieuw Unicum are routinely enrolled in neuropsychological examination as part of standard clinical care. Between January 1st 2013 and September 9th 2015, fifty-one patients with clinically definite MS were assessed. From this group, fourty-four

patients were selected for the current study based on the following criteria: absence of comorbid neurological diagnoses (excluded n=3: encephalitis, epilepsy, arteriovenous malformation), and absence of current psychiatric diseases other than depressive symptoms (excluded n=3: bipolar disorder, psychosis).

Year of diagnosis and disease type was derived from the medical status. All patients staying at Nieuw Unicum are disabled to such an extent that they require assisted living, with EDSS (Expanded Disability Status Scale) scores ranging from seven to nine (as judged by Nieuw Unicum's chief physician, author JK, M.D.). Level of dependency of support was defined by either permanent or temporary status of assisted living.

In addition, thirty-five community-dwelling control participants were recruited and matched to the patient group for age, sex and dexterity. Educational level was rated using a seven-point coding scale (ranging from less than primary school to university degree). All control participants reported no history of neurological diagnoses or current psychiatric diseases. Absence of mood disorders was confirmed by scores below cut-off on the (Dutch version of the) Hospital Anxiety and Depression Scale (HADS).[17]

All participants reported normal (or corrected to normal) visual acuity and absence of colorblindness. Participants were treated in accordance with the declaration of Helsinki. Written informed consent and approval by the local ethical committee were obtained.

Materials

A comprehensive neuropsychological test battery was administered, see table 4.

To assess perceived severity of disease symptoms and impact of these symptoms, the Multiple Sclerosis Impact Scale (MSIP) was administered.[31, 32]

Statistical analysis

The present study entailed a cross-sectional between-group design, comparing patients with MS to matched control participants. A criterion level for significance of .05 was used, with Bonferroni correction where appropriate. To indicate the size of the effects, the *partial* η^2 was calculated with values of .01, .06 and .14 to be considered small, medium and large effect sizes, respectively.

Demographics and disease characteristics

To test for adequate matching, an independent-samples *t*-test was conducted to investigate the distribution of age between the two groups, a chi-squared test for gender, and a Mann-Whitney U test for educational level.

Disease impact and perceived level of disability of the present patient sample as measured with the ICF-based MS specific scale MSIP was compared with published normative data of 530 MS patients, divided into groups with RRMS and progressive MS.[31, 32]

Differences in mood between patients and control participants were tested using two-tailed independent t-tests. A correlational analysis was performed within the patient group to investigate possible relations between disease duration (corrected for age), perceived level of disability and mood on one hand, and cognitive performance on the other.

Missing data

The nature of missing data points was coded into three different factors: random, subject-related, and subject- and task-related (an interaction between subject and the task characteristics).

Overall group differences

Analyses of differences in cognitive functioning and levels of anxiety and mood between patients and control participants were tested using univariate analyses of (co) variance, with educational level as covariate.

Moderating effect of processing speed

The influence of processing speed on group differences in cognitive performance over each domain was analysed by adding processing speed (SDMT performance) as a covariate to analyses of variance in all cognitive variables between groups (patients versus control participants). Additionally, a hierarchical regression analysis was performed to investigate the contribution of processing speed compared to other cognitive variables, in terms of predictive value on group membership. Missing data points were replaced by the group mean. Educational level (expressed in z-values) was first entered as predictor by forced entry in a binary logistic regression model with patients and control participants as categorical outcome categories. Next, a composite score of all cognitive variables (mean z-value) was added to the model. Subsequently, SDMT performance was added to investigate the unique contribution of information processing speed.

Examination of patterns in cognition in the patient group

The nature and severity of cognitive impairment in the patient group were explored by examining how many patients could be classified as either cognitively preserved, mildly impaired or impaired, based on performance on the MMSE and performance on cognitive tests compared to available normative data.

First, performance on the MMSE was examined to quantify level of global cognitive decay. Although the MMSE is not normally used in MS research, it was included to provide an indication of the severity of cognitive impairment in the current sample of advanced MS patients. Scores below 27 were considered indicative of cognitive impairment, and below 24 strongly indicative of severe cognitive impairment, at the criterion level used to classify dementia.

Next, severity of cognitive problems in the patient group was classified using existing normative data. Patients were considered cognitively preserved when performance did not exceed one standard deviation below the mean in more than one domain, as mild cognitively impaired for more than one standard deviation below the mean in at least two domains, but less than two standard deviations below the mean in two or more domains, and as cognitively impaired when performance in two or more domains exceeded two standard deviations below the mean. Dissociations between performance in the domain of information processing speed and other cognitive domains were examined, in particular whether dissociations could be found between decreased speed of information processing and performance in other domains.

Results

Demographical variables

Patients and control participants did not differ significantly on the matching variables age, gender and dexterity ($p > .05$, see table 1). As the distribution of educational level did differ between groups, this variable was used as covariate in all main analyses.

Table 1 MS Patients and Control Participants' Demographics

Variable	Patients *N = 44*	Control participants *N = 35*	*p*
Age (M ± SD)	53.41 ± 9.04	52.14 ± 8.24	.522
Gender (% male)	43 %	46 %	.822
Dexterity (% right-handed)	87 %	91 %	.557
Educational level (median, IQR)	6 (4-6)	6 (6-6)	.007*

Note. Differences were tested using chi-square (gender, dexterity), Mann-Whitney U (educational level) and two-tailed independent t-tests (age). *$p < .05$

Patient characteristics

Most MS patients were diagnosed with either PPMS or SPMS (see table 2). Disease duration of the patients ranged from 1 to 40 years, median = 19 (IQR 13-23), and was not significantly correlated with cognitive performance, corrected for age ($p > .003$, corrected for multiple comparisons). All patients were temporarily or permanently dependent on clinical care, requiring 24/7 monitoring due to their disabilities.

Table 2 MS Patients' Characteristics (N = 44)

Mean disease duration in years (SD)		**18.9**	**(8.2)**
Disease course (n)	Relapsing Remitting	2	(4.5 %)
	Secondary Progressive	19	(43.2 %)
	Primary Progressive	11	(25.0 %)
	Unknown	12	(27.3 %)
Dependency (n)	Permanently institutionalized	16	(36.4 %)
	Temporarily institutionalized	28	(63.6 %)

MSIP scores (on disease impact and perceived level of disability) in the current sample of MS patients with high EDSS scores, ranging from 7 to 9, were comparable with other progressive MS patients, except the disease impact on activities of daily living was higher (see table 3). None of the eighteen cognitive variables were significantly correlated with disease impact (tested using Kendall's Tau-b, $p > .003$, corrected for multiple comparisons).

More severe depressive symptoms and higher levels of anxiety were reported in the MS patients compared to control participants (see table 4). Mood and anxiety were not significantly correlated with any cognitive variable in the patient group ($p > .003$).

Table 3 Disease impact and disability perception in the present patient sample (N = 44) compared with normative data (N =530 multiple sclerosis patients)

	Disease impact			**Disability perception**	
MSIP[a] scale	**Sample**	**Norm**	**Norm**	**Sample**	**Norm**
		progressive MS	RRMS		
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Muscle and movement functions	7.1 (3.6)	6.2 (3.2)	2.1 (2.5)	5.2 (3.8)	4.4 (3.2)
Excretion and reproductive functions	5.9 (3.8)	4.5 (3.0)	2.1 (2.4)	3.6 (2.5)	3.1 (2.5)
Mental functions	3.4 (2.0)	2.9 (2.1)	2.0 (1.8)	2.8 (2.0)	2.5 (2.1)
Basic movement functions	10.9 (4.4)	6.2 (4.7)	1.9 (3.3)	7.0 (5.5)	4.1 (4.4)
Activities of daily living	19.5* (4.7)	10.7 (7.3)	3.3 (4.8)	11.0 (7.7)	6.4 (6.7)
Participation in life situations	7.7 (5.2)	4.6 (4.6)	1.4 (2.6)	4.1 (3.6)	2.7 (3.3)
Environmental factors	3.1 (3.3)	3.2 (3.3)	5.0 (3.5)	1.1 (2.0)	0.5 (0.0)

Note. a) MSIP = Multiple Sclerosis Impact Profile. The MSIP distinguishes two dimensions: disease impact and disability perception. The patients do not only rate the severity of their disabilities (disease impact), but also how problematic the patient perceives the reported disabilities (disability perception). An example question of the first dimension is: "do you face loss of your muscle power functions?" followed by five-level Likert-type scale ranging from "no, not at all" to "yes, I have a complete impairment". Next, the question on disability perception is posed as: "if yes, do you perceive this impairment as problematic?", with four response options ranging from "no, never" to "yes, always". * sample M > 1SD > M of the norm group of progressive MS patients. All other values lie within the normal range compared to the (progressive MS) normative data (mean difference < 1 SD)

Table 4 Group Differences between Patients (N = 44) and Control Participants (N = 35)

		Patients		**Control participants**			
Domain	**Test**	***M***	***SD***	***M***	***SD***	***p***	η_p^2
General cognition	MMSE	26.6	3.8	29.7	0.6	<.001*	.163
Processing speed	SDMT	25.9	12.5	61.8	8.3	<.001*	.715
Retrospective	(D)AVLT immediate recall	30.0	11.4	47.9	9.2	<.001*	.369
Memory	(D)AVLT delayed recall	4.9	3.5	9.6	2.8	<.001*	.306
	(D)AVLT delayed recognition	26.7	3.3	29.3	0.7	<.001*	.150
	VAT	10.6	2.5	11.9	0.4	.014	.077
Prospective memory	Event-basedPM	35.1	40.5	90.7	9.7	<.001*	.410
	Time-based PM	2.3	1.2	2.9	0.4	.013	.079
	Time monitoring	2.1	1.6	2.8	1.3	.094	.036
Attention/	PASAT	34.3	14.4	47.2	10.2	.002*	.179
Executive	BADS zoo	7.2	5.3	12.0	3.9	.001*	.155
Functioning	COWAT Letter fluency	9.1	4.8	18.2	5.6	<.001*	.406

Table 4 Group Differences between Patients (N = 44) and Control Participants (N = 35) (continued)

		Patients		Control participants			
Domain	**Test**	***M***	***SD***	***M***	***SD***	***p***	η_p^2
	COWAT Categorical fluency	24.8	10.7	44.4	11.5	<.001*	.432
Language	BNT	78.3	8.2	85.1	4.4	<.001*	.148
	WAIS Proverbs	80.0	27.3	90.0	14.8	.279	.015
Visual perception	CORVIST	22.7	2.1	23.8	0.5	.013	.079
Visual construction	CAMDEX clock drawing	2.5	0.6	2.7	0.4	.090	.046
Praxis	GIAT	14.9	4.5	19.2	1.0	<.001*	.295
Mood	HADS depression	5.8	5.0	1.5	1.3	<.001*	.204
	HADS anxiety	6.2	5.0	3.7	1.9	.012*	.082

Note. Differences on cognitive variables were tested using univariate analyses of (co)variances, controlling for educational level. Differences in mood were tested using two-tailed independent t-tests. MMSE = Mini-Mental State Examination; SDMT = Symbol Digit Modalities Test, oral version; (D)AVLT = (Dutch) Auditory Verbal Learning Test; VAT = Visual Association Test; PM = naturalistic prospective memory, PASAT = Paced Auditory Serial Addition Test ISI 2.4 seconds; BADS zoo = Behavioural Assessment of Dysexecutive Syndrome 'zoo map' subtest; COWAT = Controlled Oral Word Association Test 'animals' and 'N'; BNT = Boston Naming Task short version; WAIS proverbs = comprehension of five proverbs, based on subtest Comprehension of the Wechsler Adult Intelligence Scale III: of the number of correctly completed proverbs, the percentage of proverbs that were correctly explained was used for evaluation; CORVIST = Cortical Vision Screening Test Shape Discrimination, Fragmented Numbers and Face Perception subtests; CAMDEX: clock drawing test of the Cambridge Examination for Mental Disorders; GIAT = Goldenberg Ideomotor Apraxia Test hand positions; HADS = Hospital Anxiety and Depression Scale.[18-30] For the PASAT, BADS zoo, Clock drawing test and GIAT, caution is needed in interpretation of the (size of) the differences, as a substantial proportion of patient data was missing. * $p < .003$, Bonferroni corrected for multiple comparisons for cognitive variables, for mood * *indicates* $p < .05$

Missing data

Most missing data points were due to insufficient motor capacity (of the upper extremities) of MS patients to perform tasks that required writing or drawing. For this reason, fourteen patients did not perform the Clock drawing test, and eleven patients did not perform the BADS Zoo Map test. For eleven patients, scores on the MMSE were extrapolated as not all items of this task were assessed, according to administration guidelines.[18] Nine patients could not perform the GIAT with either hand, for six patients scores of one hand were extrapolated. Twenty-eight patients were not able to correctly perform practice trials of the PASAT test, and therefore execution of this task was aborted. Remaining missing data represented less than 1 % of the total data points.

Group differences in cognition

Patients performed worse than control participants on almost all cognitive variables, including the domains of processing speed, memory, attention/executive functioning,

language and praxis (see table 3). Overall, effect sizes were large (*partial* $\eta^2 > .14$). Significant results with medium effect sizes (> .06) were found for verbal delayed recognition memory, complex planning and naming. No significant differences were detected in the domains of visual perception and construction.

Moderating effect of processing speed

When correcting for processing speed, by adding SDMT performance as covariate to analyses of variance between patients and control participants for each cognitive variable, no significant group effects remained detectable ($p > .05$).

Hierarchical binary logistic regression model assessment further showed that information processing speed had significant predictive value over cognitive performance in other domains on group membership (patients versus control participants). Compared to the model including only the constant, the change in odds ratio after adding educational level was significant ($p = .006$), and also after adding overall cognition (mean z-value of all cognitive variables. $p < .001$) and subsequently SDMT performance ($p < .001$). Overall, the model in the last block correctly classified 96.2 % of the participants. The initially significant effect of overall cognition was obliterated after adding SDMT performance to the model, which remained the sole significant predictor in the final model, $B = 10.45$ (*SE* 4.69), $p = .026$.

Table 5

	-2LL	χ^2	R^2	**% correct**
Constant	**108.49**			**55.7**
Step 1: Education	101.03	7.46*	.12	60.8
Step 2: Cognition	38.86	62.18**	.79	86.1
Step 3: Processing Speed	15.45	23.40**	.93	96.2

Note. *$p < .05$, **$p < .001$. Nagelkerke R square is reported here.

Characteristics of cognition in the patient group

The nature and severity of cognitive problems in the MS patients was further explored.

First, performance on a global cognitive screening task, the MMSE, was examined to quantify level of cognitive decay. In the patient group, 36 % (n = 16) of MMSE scores fell below 27, indicative of cognitive impairment. Nine of these patients scored below 24, indicating severe cognitive impairment and strongly indicative of dementia. The other 64 % fell within the normal range of performance (≥ 27).

Second, classifying patients based on their performance over all cognitive domains compared to normative data, two patients were classified as cognitively preserved, 16 % (n = 7) of the patients were mild cognitively impaired and 80 % (n = 35) were cognitively impaired, to such an extent they fulfilled the cognitive criteria for dementia.

In most cases (thirty), speed of information processing was decreased (SDMT and/or PASAT performance >2SD below the mean), accompanied with deficits in other domains. Five patients, classified as mild cognitively impaired, were only impaired on information processing speed. Four of those patients did show below average performance (>1SD below the mean) in other domains (executive functioning, memory, language). Two patients showed cognitive impairment only in other domains (memory, language) without deficits in speed of information processing, one of whom did show below average SDMT performance.

Discussion

The current study provides insight in the patterns of cognitive deficits in a previously largely neglected group of patients with MS: those in advanced stages of the disease with severe disabilities to such extent that they are unable to maintain independency. These patients displayed severe and widespread cognitive deficits, more than usually described in MS, including functions that are usually thought to remain intact.[1, 9] This implies that data and recommendations from literature biased towards earlier disease stages are not necessarily applicable to more disabled patients.

In the patient group, decreased performance was found in general cognitive abilities, speed of information processing, memory, attention/executive functioning and praxis, compared to age- and gender-matched control participants, controlled for educational level. Effect sizes were medium to large. Importantly, the affected functions included those that are not usually associated with MS, such as recognition memory and language (anomia).[2, 33] No less than 80 % of the patients (thirty-five/forty-four) fulfilled the cognitive criteria for major neurocognitive disorder based on the DSM-5. Nine patients (20 %) performed at such a low level of global cognitive functioning that in severity is similar to neurodegenerative diseases such as Alzheimer's. These results ask for clear guidelines regarding the definition and diagnosis of dementia in MS patients, but this remains rarely discussed.[34]

Information processing speed was shown to be an important factor determining cognitive functioning in the current sample, in congruence with previous research.[6] In

almost every patient, information processing speed was affected. Whether information processing speed causes disturbance in other domains or these are separate parallel processes is hard to disentangle, as the tests that measure the different cognitive functions are not independent.

Patterns of impairment in other domains than processing speed varied between patients. Therefore, it is important to depict which specific cognitive functions are affected in individual MS patients to pinpoint treatment focuses in clinical settings. Accordingly, it is recommended to include all major cognitive domains in neuropsychological assessment in MS.

The combination of severely diminished processing speed along with disturbances in most other domains could reflect overall cognitive decay, suggestive of a 'network collapse'.[35] The abnormalities might result from subcortical as well as cortical damage. Imaging data should be collected to gain understanding of the underlying neural correlates, preferably comparing patients with MS in different stages of the disease course. Of particular interest would be connectivity analyses, to test the 'network collapse' hypothesis, and the relative contribution of white versus grey matter involvement to different aspects of cognition (contrasting 'global' cognitive functions such as processing speed with 'focal' functions like memory recognition).[5, 14]

In the current study, not for all cognitive functions decreased performance was detected. This could indicate that those functions are not affected in MS, could partly be caused by missing data points e.g. due to motor demands of some tasks, or tasks targeting these functions were not sufficiently sensitive to detect group differences. With respect to the latter, data were collected within standard clinical care, and some tests were more suitable for qualitative interpretation than for quantitative analysis necessary for research purposes. For the regression analyses standard deviations were probably suppressed because missing data were replaced by the group mean, which may have influenced the outcome. Although the test battery was composed to be considerate of patients' sensory and motor difficulties, physical symptoms of MS may have confounded cognitive performance.

A strong point of the study is the selection procedure. All patients who were admitted to the clinic were included without bias by selection of patients with cognitive complaints. However, as patients who received prior neuropsychological evaluation were not included, severity of cognitive problems in the target population could be underestimated. The range of disease duration was rather wide (1-40 years), which shows that progression of the disease occurs at different rates. Disease duration was not

significantly correlated with cognition. In the current study, no distinction in subgroups with different disease courses was possible due to limited sample size. Differences in pathology between RRMS, PPMS and SPMS have been widely studied. However, differences in their cognitive performance are less extensively investigated. Possibly, in the advanced stage, differences between disease types become less pronounced. The current sample of patients even included two patients who are still classified with RRMS, whereas they clearly show severe chronic disabilities. Follow-up studies may focus on differences between disease subtypes in the long haul, and neural correlates of cognition in these patients.

Disease impact in the selected patient group was largely similar to other progressive MS patients, but more restraints in activities of daily living were reported.[31, 32] This is congruent with the setting where they resided, being dependent on clinical care. No correlations between disease impact and mood with cognition were found in the patient group. Possibly, this can be explained by decreased meta-cognitive abilities and awareness in patients with increasingly severe cognitive deficits. This would increase risks of over- as well as underestimation of cognitive abilities, especially in settings such as nursing homes where MS is still largely considered a somatic disease with primarily physical symptoms. Psychiatric symptoms are often overlooked in MS.[33] Therefore, in this particularly vulnerable patient group, it is important to objectively monitor both mood and cognitive abilities to provide suitable care.

To conclude, cognitive functioning in MS can be severely disturbed. Reduced speed of information processing is prominent, and it remains a crucial factor determining overall cognition in advanced stages of the disease, where a broad range of domains can be affected.

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8

Summary

The aim of this thesis was to better understand the cognitive architecture underlying complex functions that are relevant for daily life. A special focus was placed on prospective memory (PM), which is a particularly interesting subject of study as it involves many components.

PM is defined as remembering to carry out intended actions at an appropriate moment in the future. This moment can either be coupled with a specific time (time-based, TBPM) or when a specific event occurs (event-based or EBPM). It involves multiple cognitive operations, including the formation of an intention, remembering the intention over a delay period, monitoring when and how to execute the intention and performing the intention (McDaniel & Einstein, 2011). It encompasses both retrospective (remembering what action was to be performed) and prospective components (maintaining and executing the action).

In **chapter two**, it was investigated how PM is affected in dementia and its prodromal stage MCI (mild cognitive impairment), conditions characterized by memory impairments. Patients with these conditions often complain more about their memory with respect to future actions (PM) than about retrospective memory (RM) failure, although research on PM is much more limited and it is rarely included in clinical neuropsychological assessment. A meta-analysis of thirteen studies showed that both MCI and demented patients show large PM deficits, both in EBPM and TBPM, prospective as well as retrospective components. The few studies investigating the cognitive correlates of PM in these conditions indicated that executive functions, such as planning, and RM seem to be related to PM functioning. The findings of this meta-analysis stress the importance of regarding PM as a relevant aspect of cognitive dysfunctioning, particularly because PM is often severely affected in dementia and even already in MCI patients.

In **chapter three**, we delineated what cognitive functions are involved in prospective memory. We found that EBPM and TBPM could be selectively impaired in stroke patients, indicating that these aspects of PM are dissociable. Also, we observed differences in their cognitive correlates (see figure 1): our EBPM task was shown to involve a relatively simple and automatic process, supported by retrospective memory functioning. TBPM was found to be more complex, and involved recruitment of several cognitive functions: information processing speed, attention/executive functioning and retrospective memory. An explanation for differences in cognitive complexity between EBPM and TBPM is that EBPM by definition involves an external cue that should automatically evoke retrieval of the intention, whereas TBPM requires self-initiated retrieval which demands more effort. Active monitoring behavior was related to better TBPM performance. Those participants who more often checked a watch to monitor how much

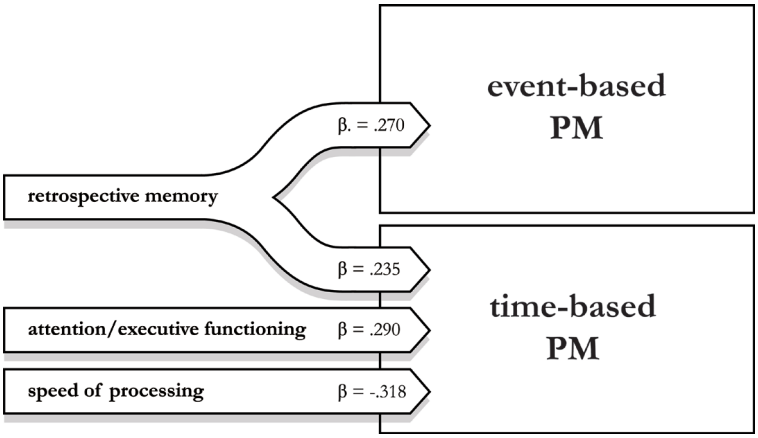

Figure 1. *Contributions of cognitive functions to event-based versus time-based prospective memory (Kant et al., 2014)*

time had passed, were better able to execute the intended action at the right time. Compared to healthy participants, patients showed less active monitoring. In that perspective, perhaps monitoring could be a specific target in rehabilitation programs for patients who suffer from PM problems.

From investigating the consequences of dementia for PM and functional dissociations in stroke, we learned that PM is a clinically relevant and cognitively complex construct. Therefore, we were keen to validate theories on cognitive correlates of PM. To this aim, in **chapter four**, we performed a confirmative analysis of ideas based on previous explorative experimental research. Using Bayesian statistics, we tested several alternative hypotheses on the differential contribution of sequential processes, visuospatial processing and vigilance in TBPM versus EBPM. However, none of the formulated hypotheses gained support over the null-hypothesis that none of these variables contributed to PM performance. Exploratory analyses, however, did show involvement of several of these processes in PM, and dissociations between EBPM and TBPM, in congruence with the results of chapter three. Verbal working memory, time perception and monitoring were associated with TBPM, and ongoing task behaviour predicted EBPM performance. More than providing firm answers, this study generated new questions about the cognitive architecture of PM. One lesson we learned was that there remains much more to know about the interplay of cognitive processes in PM and what constitutes these processes on their own, before more solid theories can arise. We therefore further investigated several of these processes thought to be related to PM in chapters five and six: spatial and temporal order memory and time perception.

In **chapter five**, dissociations between spatial and temporal order memory were examined in stroke patients. Spatial and temporal order memory seem to be closely related. In trying to remember a route the locations where you see landmarks are important, but also in which order these landmarks are perceived. Still, by demonstrating that these two aspects of contextual memory (spatial location and temporal order) can be differentially affected in stroke, we concluded that they are dissociable. Seven patients (18%) showed selective impairment in either remembering the spatial location of recently shown objects, or the order in which these were presented. Also, we found evidence for lateralization of temporal order memory to the left hemisphere. This is in line with ideas that the left hemisphere contains a sequential processor (Nicholls, 1996). As no laterality effects were found on memory for spatial location, both the left and right hemisphere might be recruited to solve this task, showing flexibility of the brain to adapt to the task at hand.

In **chapter six**, we investigated how different cognitive functions are related to time perception. Different dimensions of time perception were tested using a paradigm where subjects were either asked to estimate the duration of a tone, to reproduce a sample tone or to produce tones of a pre-specified length (in seconds). Seven stroke patients (19%) showed time perception deficits, and dissociations were found between different task dimensions (estimation versus reproduction of time intervals). How people perceive the passage of time was shown to be correlated with (working) memory and information processing speed. These results are in congruence with literature stating that adequate sense of time for durations in the seconds range depends on the integration of timing with other cognitive processes, through interactions between subcortical and cortical regions in the brain. When either of these regions is affected, distortions can arise.

In the studies performed in the stroke population we focused on finding dissociations by contrasting performance on different cognitive tasks in patients with focal brain damage. In the last experimental chapter (**chapter seven**) we shifted towards a condition with more diffuse brain damage: multiple sclerosis (MS). More specifically, a group of MS patients with severe disabilities was investigated. This group, despite their probably extensive brain damage, has been largely neglected in the literature on cognition in MS. Moreover, especially in this group it is important to provide patient-tailored care to meet their needs. We found that cognitive deficits in these patients are severe and widespread. Cognitive functions that were found to be affected included retrospective and prospective memory, attention and executive functioning, and in particular information processing speed. Notably, speed of information processing largely determined performance in the other cognitive domains. With this study, we made an attempt to

not only describe whether cognitive functions are affected in advanced MS, but also how.

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9

General discussion

The results of the studies described in this thesis show how functions of the brain can be differentiated and how they work together. By studying the cognitive consequences of disruptions caused by brain damage, I learned about the characteristics of prospective memory (PM), contextual memory and time perception.

Existing theories on PM acknowledge that it is a complex construct involving multiple components (McDaniel & Einstein, 2011). To adequately form an intention to perform a certain action, remember it over time and execute it at the appropriate moment, several cognitive functions are recruited. The results from our studies showed that event-based and time-based PM (EBPM and TBPM) differ in their cognitive architecture. As EBPM involves an external cue, retrieval is automatically probed, and it is supported by retrospective memory (RM, to recall what intention was to be performed). TBPM, requiring time monitoring and self-initiated retrieval, is more cognitively complex: it is supported by information processing speed, attention/executive functioning and retrospective memory (Kant et al., 2014). Using Bayesian statistics, I tried to further delineate the cognitive architecture underlying PM. One of the assumptions we tested was that time perception and other sequential processes such as temporal order memory would be more involved in TBPM than in EBPM. We did find an indication for the involvement of time perception in TBPM, but our specifically stated hypotheses were not supported by the data (unpublished data). Therefore, my ideas have to be revised. There apparently is still much more to learn. By further studying contextual memory (for spatial location and temporal order) and time perception I did gain better understanding of these functions. Still, the prospective memory construct remains difficult to grasp and disentangle into well-defined parts. It does not fit in classical domain subdivisions and is not easily regarded as a separate function because of its cognitive complexity. It can however be selectively impaired in the absence of obvious other cognitive deficits. PM may link with many cognitive functions, but also plays its own part in the human neurocognitive system. It should be regarded as a unique and relevant construct, although it is still in need of further definition.

In this thesis, several populations, both in health and disease, were recruited to answer the postulated research questions, using a variety of statistical methods: from exploratory to confirmative.

First, we performed an exploratory meta-analysis to investigate the magnitude of PM problems in patients, to stress the relevance to study the PM construct. As studies on PM are still limited, spurious results can easily occur and these can cloud judgements. Meta-analysis is a powerful method for combining multiple independent (and in many cases relatively small) association studies. It provides not only information on a pro-

posed association, but also on the strength of such an association. Combining results from previously collected data provided more reliable information, demonstrating that PM is often affected in MCI (mild cognitive impairment) and dementia. Also, we derived information on the extent to which these problems were present by calculating overall effect sizes, showing large effects for both patient groups.

Next, we explored functional differentiation and interactions by applying both single case statistics and regression analyses, making use of the specific characteristics of different patient populations. From the stroke population with selective focal damage we could learn what functions are needed to perform a certain cognitive task. We used a case study approach to study individual patterns. Statistical procedures were used that are specifically designed to control inflated (type I) error rates and overestimation of the abnormality of patients' scores (Crawford & Howell, 1998). These analyses were informative to detect functional dissociations between TBPM and EBPM, time estimation and reproduction, and spatial and temporal order memory. Regression and correlational analyses additionally showed how several cognitive functions are connected with each of these processes. In patients with extensive overall damage caused by multiple sclerosis (MS), relations between different cognitive functions were also investigated by regression analyses, showing a central role for information processing speed. By statistically disentangling these associations a clearer view was obtained on the mediating effect of information processing speed.

To put ideas that arose from explorative studies on PM to the test, confirmative analyses using a Bayesian model selection approach were performed in healthy participants. Instead of traditional null-hypothesis testing, with Bayesian statistics you test what you want to know by stating informative hypotheses. Bayesian statistics provide a unique opportunity to directly compare differential hypotheses. By applying these stringent methods to search for confirmation of specifically stated assumptions with regard to the role of different cognitive processes in EBPM versus TBPM (but not finding support for the formulated hypotheses), we learned that theories on PM should be further developed.

All of the methodological approaches that were used in this thesis are thus complementary to each other. I therefore want to make the case for a multi-methods neuropsychology. We learn in different ways from different people. We look back to learn in retrospect, and think ahead of new approaches and future directions.

In the future, in addition to further investigation of fundamental research questions, the development of suitable diagnostic instruments to assess the specific problems

patients are faced with should be an important focus in PM research. However, it is difficult to include PM in clinical neuropsychological assessment, as instruments to assess it are scarce and usually not very suitable (Shum, Fleming & Neulinger, 2002). Tasks used for research purposes are often too time consuming and/or difficult for application in practice or lack ecological validity, whereas available clinical tasks do not show sufficient psychometric qualities to fulfill diagnostic standards. Particularly challenging is that PM cannot not be assessed on its own, but while performing an ongoing task. Distribution of experimental trials over the ongoing task should be sufficiently spread out, and not too predictable. This would require a relatively lengthy task, which is difficult considering clinical demands. With my colleagues, I strived to develop a new instrument to assess EBPM suitable for clinical use, using a paradigm that was integrated within standard neuropsychological assessment, and applied it in one of our studies (chapter seven). Participants were instructed to summarize each test in the assessment in a single keyword after it had ended (a cue was provided). This procedure required no specific filler tasks, making it particularly useful in clinical practice. It was feasible, for example patients were able to follow the task instructions. Also, they did show lower performance compared to control participants, indicating discriminative ability. We also piloted a TBPM variant, where participants were instructed to indicate to the neuropsychologist that 30 minutes had passed every half hour from the start of the assessment. However, in the pilot phase of this time-based procedure, signs of potential interference with performance on the ongoing tests were observed (i.e. one participant indicated in the middle of a verbal memory task that 30 minutes had passed). We aborted this endeavor as it seemed to confound performance on the other tests. Designing a PM task that is clinically applicable is ultimately particularly difficult when the PM construct is still not clearly delineated. I see this attempt as a beginning to experiment with new applications for clinical practice.

In addition to the development of clinically suitable PM tasks, test material to assess contextual memory and time perception should also be further investigated on its clinical applicability. Validity and reliability analyses are required to implement paradigms used in scientific research (such as those described in chapters five and six) in clinical practice. Adaptations should be made in task characteristics to actualize sufficient sensitivity and specificity for diagnostic purposes, at the same time keeping task demands low enough for patient populations and considering time constraints of clinical neuropsychological assessments including multiple domains. Also, diagnostic standards are necessary. In particular, the results of our MS study call for development of criteria to classify the severity of cognitive impairment in MS. The question of how to determine whether cognition is affected to such an extent to speak of the presence of MS dementia should be addressed (see also Westervelt, 2015).

In times where more and more focus is directed towards imaging research (studying cognition at the structural level), it remains crucial to investigate what happens at the behavioral level. To know where a function is located, does not tell you how it functions. Knowledge on cognitive processing is gained by studying how functions interact, differentiate and how they are affected by brain damage. In answering these questions, lesion studies and the method of functional dissociation still have unique value. Only when you know what a function entails, you know where to look for underlying neural mechanisms. As Lezak (2004) states: 'even when the site and extent of a brain lesion have been shown on imaging, the image will not identify the nature of residual behavioral strenghts and the accompanying deficits: for this neuropsychological assessment is needed'.

Structural and behavioral data complement each other. Both can lead to questions that can be answered by the other, and combining them will ultimately lead to better knowledge of brain functioning. One striking example that shows the importance of this combination is the case of H.M., or Henry Molaison (1926-2008), the world's most famous memory patient (first described in 1957 by Scoville and Milner). Henry suffered from significant memory loss after removal of hippocampal tissue to cure his epilepsy. Behavioral observations during his life revealed dissociations between distinct memory functions. While Henry could retrieve information from before his surgery, and was able to have a normal conversation about what happened in real time (working memory) he was not able to recall recent information (of minutes before). The hippocampus was appreciated to be crucial for the consolidation of new information into long-term memory. After Henry deceased in December 2008, the scientific community was eager to gain more insight in the structural damage underlying his memory problems, by dissection of his brain. The dissection even was live streamed, which I followed with curiosity: it was a hot topic in the period while I was doing my neuroscience research masters internship. The post-mortem structural data (MRI, 3D reconstruction) indeed provided exciting new findings (Annese et al., 2014). Especially interesting was that a formerly undetected lesion in the frontal cortex was revealed. The single most important question that subsequently arose was: how does this relate to the behavior that Henry showed? The focus shifted back from structural data to behavioral data, that was mostly collected by neuropsychologist dr. Suzanne Corkin (see for example Corkin, 1984). Unfortunately, as came in the news in August 2016, dr. Corkin seemed to have shredded parts of the original material before she passed away in May 2016. Some of the puzzling questions may thus always remain unanswered.

To pose questions on the relation between structure and function and to have them answered is the ultimate goal for neuropsychologists. Obviously though, most answers then lead to new questions: the neuropsychological researcher is never finished…

Several questions that arose from the studies described in this thesis concern the relation between structure and function. This is the core of neuropsychology: the relation between brain and behavior. Examples of these questions based on our results asking for further study are:

- What role does the superior temporal gyrus play in the neural mechanisms underlying PM, as it was shown to be affected often in patients who show selective PM deficits?

- How is temporal order memory moderated by the left hemisphere?

- How do subcortical (basal ganglia) and cortical (supplementary motor area, prefrontal cortex) brain areas collaborate in supra-second time perception in relation to other cognitive processes?

- How do white and grey matter pathology in advanced MS patients contribute to 'global' cognitive decay and 'focal', more specific, cognitive deficits? Does cognitive impairment in advanced MS reflect a 'network collapse'?

One of my first future goals is to address this last question and thereby to bring together research on structure and cognitive functioning in advanced MS. The results of the study described in this thesis showed that a multitude of functions can be affected in advanced MS, with a central role for information processing speed. The next question is how this relates to brain damage in these patients. In recent years, MS imaging research has shown a prominent role for grey matter damage in MS, in addition to the well-known white matter pathology that never seemed reliably correlated with cognitive dysfunctioning (Calabrese, 2006). At the same time, studies of brain network dysfunctioning by advanced imaging methods such as connectivity analyses seem promising (see for example Hulst et al., 2015). Possibly, combining imaging with neuropsychological assessment in advanced MS may lead to better understanding of the differential contribution of different aspects of neuropathology to cognition, thereby increasing comprehension of the nature of cognitive dysfunctioning in MS. This would help to direct treatment strategies.

We live in exciting times, with lots of opportunities to investigate cognition, with many technological and theoretical advances that could bring ever new answers. If only the right questions are being asked… Curious minds like mine are thrilled to explore and take the field further and further in the future. Perhaps many of the ideas posed in this thesis will soon be obsolete, but I am sure that as they go many new ideas will arise that we will be even more excited about.

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Nederlandse samenvatting

"Een lichaam is een eenheid die uit vele delen bestaat; ondanks hun veelheid vormen al die delen samen één lichaam (...). Het oog kan niet tegen de hand zeggen: 'Ik heb je niet nodig,' en het hoofd kan dat evenmin tegen de voeten zeggen."

1 Korinthiërs 12: 12 & 21

Mensen denken meestal niet bewust na over hoezeer hun gedrag wordt aangestuurd vanuit het brein. Het lijkt vanzelfsprekend hoe je bijvoorbeeld een kopje koffie drinkt. In werkelijkheid zijn hier vele hersenprocessen mee gemoeid. De verschillende functies van het brein zijn afhankelijk van elkaar, op eenzelfde manier als je lichaamsdelen. Pas wanneer een deel van het systeem uitvalt, beseffen we hoezeer we afhankelijk zijn van het goed functioneren van het geheel. Bijvoorbeeld toen ik een schouderblessure had kreeg ik pas door dat je niet alleen je handen gebruikt om te schrijven. Zo gebruiken we ook niet alleen ons geheugen om zaken te onthouden. Daarvoor is efficiënte samenwerking nodig tussen hersenfuncties. Cognitieve functies zoals aandacht en geheugen werken niet op zichzelf, maar als onderdeel van complexe neurale systemen. Toch speelt elk van deze functies ook een eigen rol in het geheel. Ook al heeft je voet je hand nodig om je schoenen vast te knopen, zij hebben beiden hun eigen functie.

In dit proefschrift worden verschillende functies van het brein onderzocht vanuit neuropsychologisch perspectief. De neuropsychologie is een relatief jonge discipline die zich bezighoudt met de relatie tussen hersenen en gedrag (Deelman & Eling, 2007). Een belangrijk onderdeel daarvan is het onderzoeken van functiespecialisatie binnen het brein, door het bestuderen van patiënten met selectieve schade aan de hersenen. Een van de kernmethoden is het beschrijven van dissociaties. Wanneer aangetoond kan worden dat een patiënt uitvalt op een bepaalde functie (A), waarbij een andere functie (B) intact blijft, en andersom (wel B, maar niet A is aangedaan), dan kan worden gesteld dat aan deze functies verschillende mechanismen ten grondslag liggen. In de wetenschappelijke studies die beschreven staan in dit proefschrift heb ik me gericht op interacties en dissociaties tussen verschillende cognitieve functies. Het doel daarvan was om hersenfuncties die relevant zijn voor het dagelijks leven beter te begrijpen. De focus ligt op het prospectief geheugen, wat bij uitstek een functie is die complex is en waarvan nog niet duidelijk is wat de onderliggende cognitieve architectuur is.

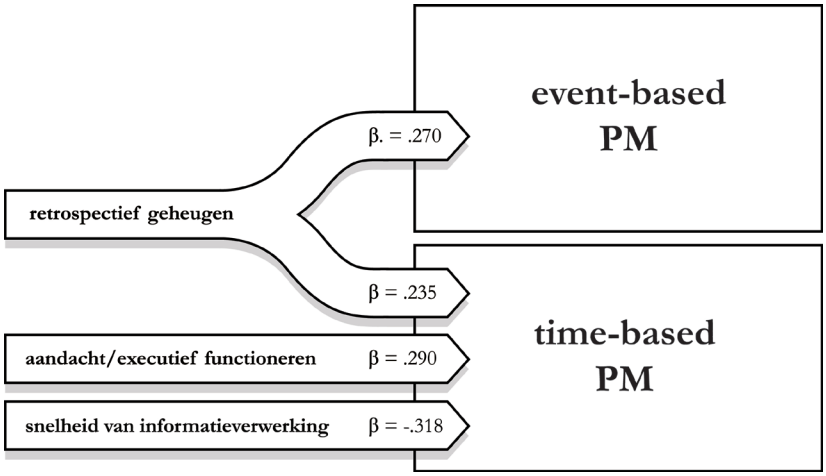
Het prospectief geheugen is het vermogen om voorgenomen handelingen te onthouden (McDaniel & Einstein, 2011). Deze kunnen gekoppeld zijn aan een bepaalde tijd, bijvoorbeeld op 11 januari om 12.45 uur stipt aanwezig zijn in het Academiegebouw, of aan een bepaalde gelegenheid zoals niet vergeten augurken mee te nemen als je in

de supermarkt staat. Je moet ervoor vooruit kijken (het prospectieve component: de intentie actief houden en op het juiste moment uitvoeren) en terugblikken (om nog te weten wat het was dat je je had voorgenomen, in retrospect) (Van Den Berg, Kant, & Postma, 2012). Het is dan ook logisch dat verschillende cognitieve functies nodig zijn voor het uitvoeren van een prospectief geheugentaak en dat het kwetsbaar is voor hersenschade.

In **hoofdstuk 2** wordt beschreven in hoeverre het prospectief geheugen is aangedaan bij patiënten met milde cognitieve stoornissen en dementie. Deze patiënten staan bekend om hun geheugenproblemen, maar vreemd genoeg is het prospectief geheugen onderbelicht in de literatuur. Wij voerden een meta-analyse uit op basis van dertien studies. Daaruit bleek dat mensen al in de voorstadia van dementie (met milde cognitieve stoornissen) ernstige stoornissen in het prospectief geheugen hebben. Er was nog beperkt onderzocht welke cognitieve functies daar verder bij betrokken waren. Wel leek duidelijk dat executieve functies (zoals planning) en retrospectief geheugen (het nog herinneren van eerder gegeven informatie) belangrijk zijn voor het uitvoeren van prospectief geheugentaken.

In **hoofdstuk drie** onderzochten we welke cognitieve functies betrokken zijn bij het prospectief geheugen. Daarvoor testten we mensen die een beroerte hadden ondergaan. Elk van deze mensen heeft selectieve schade in de hersenen. Welke gevolgen dat heeft voor de cognitie is afhankelijk van welke netwerken in het brein zijn aangedaan. Door verschillen tussen deze mensen in hun cognitieve prestaties te analyseren, kwamen we achter functionele dissociaties binnen het prospectief geheugen (zie figuur 1). Het bleek dat het onthouden van een prospectief geheugentaak die gekoppeld is aan een gebeurtenis ('event-based') relatief automatisch verloopt. De gebeurtenis werkt als externe 'cue'. Bijvoorbeeld als je een brief op de post wil doen, en je loopt langs een brievenbus, dan is dat het signaal dat de intentie oproept (als het goed is...). Dan hoef je alleen nog maar je voornemen te herinneren (retrospectief geheugen) en de rest verloopt redelijk simpel. Daarentegen is het complexer als je voornemen gekoppeld is aan een tijdstip. Daarbij is er geen extern signaal dat je er aan herinnert, en is het nodig om zelf in de gaten te houden of het al zover is. Het bleek dat verschillende cognitieve functies bijdragen aan het goed uitvoeren van zo'n 'time-based' taak: snelheid van informatieverwerking, aandacht/executief functioneren (daaronder valt bijvoorbeeld het verdelen van de aandacht: 'multitasken') en natuurlijk ook hier het retrospectief geheugen. Daarnaast werd duidelijk dat hoewel het nodig is om de tijd actief in de gaten te houden (door regelmatig op de klok te kijken), de patiënten die een beroerte hadden ondergaan dit minder vaak deden. Het zou kunnen helpen als zij hierin speciaal

getraind worden. Door beter te begrijpen waar het misgaat bij patiënten, kun je gerichter zoeken naar oplossingen.



Figuur 1. De bijdrage van cognitieve functies aan 'event-based' versus 'time-based' prospectief geheugen.

In **hoofdstuk vier** voerden we een confirmatieve analyse uit op basis van ideeën uit de literatuur en de eerdere hoofdstukken over welke cognitieve processen betrokken zijn bij 'event-' en 'time-based'prospectief geheugen. We gebruikten een stringente methode: de Bayesiaanse modelselectie. Daarmee kan getoetst worden welke van verschillende alternatieve hypothesen het best aansluit bij de data. We verzamelden data bij gezonde proefpersonen over prospectief geheugen en verschillende functies die daarmee samen zouden kunnen hangen: verbale en visuospatiële aandachts- en werkgeheugenfuncties, spatiëel en temporeel episodisch geheugen en tijdperceptie. Het bleek echter dat onze voorspellingen over de samenhang tussen deze functies en het prospectief geheugen allemaal niet uitkwamen. Deze analyse riep dus meer nieuwe vragen op dan dat het antwoorden gaf. Het werd duidelijk dat het nodig was om eerst mogelijk gerelateerde functies op zichzelf nader te onderzoeken. Dat deden we in de volgende hoofdstukken.

In **hoofdstuk vijf** onderzochten we wederom (net als in hoofdstuk drie) mensen die een beroerte hadden ondergaan, dit keer om dissociaties tussen geheugen voor plaats (spatiëel) en volgorde (temporeel) te onderzoeken. Als je bijvoorbeeld een route wilt onthouden let je niet alleen op waar je langskomt, maar ook in welke volgorde; deze aspecten van contextueel geheugen lijken dus bij elkaar te horen. Toch blijken ze te dissociëren. Patiënten vielen namelijk selectief uit op taken waarbij zij van net daarvoor

getoonde afbeeldingen ofwel de plaats waar ze te zien waren moesten onthouden, of de volgorde waarin deze vertoond werden, of allebei. Sommige patiënten konden wel de plaats onthouden, maar niet de volgorde, en andersom. Het lijkt er op dat met name de linkerhersenhelft betrokken is bij het geheugen voor volgorde. Voor het spatiëel geheugen was niet zo'n duidelijk patroon van lateralisatie zichtbaar.

In **hoofdstuk zes** staat beschreven welke cognitieve functies betrokken zijn bij tijdperceptie. Verschillende aspecten van tijdperceptie werden onderzocht. Drie verschillende taken werden afgenomen: het schatten van tijdsduur van een toon, het reproduceren van een voorbeeldtoon en het produceren van een toon van een tevoren bepaalde duur. Bijvoorbeeld werd daarbij gevraagd om een toon van 12 seconden lang te produceren door een knop precies zo lang ingedrukt te houden. Er kwamen dissociaties naar voren tussen deze taken bij patiënten die een beroerte hadden ondergaan, en correlaties met taken voor (werk)geheugen en snelheid van informatieverwerking. Dat betekent dat het verwerken van tijdsduur in het brein niet op zichzelf staat maar dat er verschillende cognitieve functies bij betrokken zijn.

Na het bestuderen van dissociaties in patiënten met selectieve hersenschade na een beroerte, onderzochten we in **hoofdstuk zeven** juist een populatie met meer globale hersenschade, waarbij netwerken overal in het brein beschadigd raken: mensen met multiple sclerose (MS). Over het algemeen wordt cognitie in deze ziekte vooral in relatief mildere stadia onderzocht, en de bevindingen uit die onderzoeken (cognitie leek redelijk licht aangedaan, op enkele gebieden) strookten niet met observaties in de kliniek waar ik werk met meer gevorderde MS patiënten. Door een uitgebreide neuropsychologische testbatterij af te nemen bij deze groep werd duidelijk dat hun cognitie ernstig en wijdverbreid verstoord kan raken, in alle cognitieve domeinen. Vertraagde snelheid van informatieverwerking staat daarin centraal.

De resultaten van deze studies leidden tot nieuwe inzichten over de eigenschappen van bepaalde functies in het brein en hoe deze samenwerken. In een tijd met steeds meer technologische ontwikkelingen wordt het mogelijk om de structuur van hersenen steeds gedetailleerder in kaart te brengen. Veel onderzoek richt zich dan ook op localisatie van functie, bijvoorbeeld welke hersengebieden actief zijn bij het uitvoeren van een bepaalde taak kun je onderzoeken middels fMRI (functionele magnetische resonantie imaging, een hersenscan). Dat leert ons wáár zich bepaalde processen afspelen in het brein. Voor het beantwoorden van de vraag wát er dan gebeurt, en hoe cognitieve functies samenwerken, blijft het hard nodig om het gedrag dat voortkomt uit de hersenen te onderzoeken. Dat is de meerwaarde van neuropsychologisch onderzoek, waarmee je het gedrag zelf bestudeert. Door de gevolgen van hersenschade

voor cognitie te bestuderen en te leren van selectieve uitval na verschillende vormen van hersenletsel, kunnen we menselijk gedrag steeds beter begrijpen. Mijn missie is om met die kennis vervolgens mensen met hersenletsel gepaste hulp te kunnen bieden. Nu is het al zo dat we bijvoorbeeld door mensen met MS uit te leggen dat geheugenproblemen horen bij de ziekte, zij deze problemen beter kunnen hanteren. Ik ben voornemens om zowel het werk als neuropsycholoog in de patiëntenzorg als in het onderzoek te continueren, om die kennis te blijven vergaren en uit te dragen. Hoe meer we weten, hoe meer we kunnen!

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Dankwoord

Het voelt nog onwerkelijk dat ik vanaf 11 januari 2017 de doctorstitel zal dragen, maar ik durf mezelf ondertussen toch echt wetenschapper te noemen. Dat heb ik vooral aan mijn begeleiders te danken. Mensen kijken me meewarig aan als ze horen dat ik maar liefst 4 (co)promotoren heb, 'dat zal wel lastig zijn, om tussen alle ego's je eigen pad te kunnen vinden...' maar voor mij was het een zegen. Ieders expertise en persoonlijkheid droeg op unieke wijze bij aan het onderzoek en mijn ontwikkeling.

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Martine: voor mij ben jij een groot voorbeeld in het verbinden van kliniek en wetenschap. Al tijdens colleges in de bachelor dacht ik jaloers: dat wil ik ook. Zo gedreven en gepassioneerd voor het vak, zowel in de praktijk als het onderzoek. Wat een droombaan zou dat zijn. Jij hielp mij om tegelijkertijd masters in de klinische neuropsychologie en de neurowetenschappen te volgen. Ondertussen ken ik ook de nadelen van het continue schipperen met tijd en belangen, maar die wegen nog steeds niet op tegen de meerwaarde. Het is erg verrijkend en inspirerend om met jou te werken.

Nadat ik in eerste instantie de enige op de afdeling was die zich met het onderwerp prospectief geheugen bezig hield en daarin wat verloren was, kwam gelukkig Esther het team versterken. To-the-point, pragmatisch, helder. Waar ik de bomen door het bos niet zag, kon jij mij helpen om weer scherper te kijken, prioriteiten te stellen en knopen door te hakken. Ik bewonder je voortvarendheid en sta steeds versteld wat jij allemaal in korte tijd weet te bereiken. Wat heb ik een geluk om met de top van neuropsychologie in Nederland samen te werken.

En tenslotte Jaap: zonder jou was ons stroke onderzoek er überhaupt niet geweest. Al jarenlang wordt er nu systematisch data verzameld van stroke patiënten in het UMCU, wat een schat van informatie geeft om onze onderzoeksvragen op los te laten, en zo uiteindelijk ook de patiëntenzorg te verbeteren. Voor mij ben je altijd op een prettige en zeer toegankelijke manier voornamelijk op de achtergrond aanwezig geweest. Als ik bij jou langskwam benadrukte je altijd ook even dat het allemaal niet zo vanzelfsprekend is dat het me toch lukte om ook bij tegenslag door te gaan. Ik voelde me daardoor zeer gesteund en kon er met goede moed weer tegenaan.

Naast mijn (co)promotoren heb ik mij in mijn tijd als promovendus ook erg gesteund gevoeld door mijn collega's, zowel op de universiteit als in de kliniek.

Tijdens de research master vormden we de neuro 'leesclub' met Remko, Judy, Claudia, Saskia en Haike. Veel boeken hebben we niet gelezen, maar met jullie was het altijd gezellig. En wat een toppers zijn jullie allemaal geworden! Saskia, met jou heb ik zowel stage als docentschap gedeeld en we werken zelfs nog steeds samen in de kliniek: wat een geschenk. Ik heb veel bewondering voor jou als persoon en als neuropsycholoog.

Op de UU begon ik tussen de 'space ladies'. Het begrip ruimtelijke cognitie werd ruim opgevat waardoor ik er prima tussen paste. Dank dat jullie mij met open armen ontvingen. De gastvrijheid op de afdeling ging verder dan de wetenschap: in de vorm van 'eet & greet' hebben we veel mooie avondjes gehad met Stijn, Marijn, Elise, Sarah, Jelmer & Valentina, en later ook met Manasa, Siarhei en Miranda.

Especially with you Valentina I feel a strong connection, even though we are at times far apart. Hopefully many more visits to and from Gent and Italy will follow in the future!

Jelmer en Miranda, jullie waren vooral in respectievelijk het eerste versus laatste deel van mijn PhD mijn favoriete slachtoffers voor koffie- en borrelmomenten. Jelmer: nadat we samen de bruidssuite hebben gedeeld op de Helmholtz retraite verlaat je me constant, maar ik weet je toch wel weer te vinden. Miranda, zoals je zelf al zei: nu hoeven we elkaar niet meer te introduceren als collega's, hoewel we al veel langer wisten dat onze vriendschap verder gaat. Je bent een wonderlijk persoon, en ik hoop je nog veel beter te leren kennen.

Onmisbaar voor eigenlijk alles wat met het reilen en zeilen op de afdeling te maken heeft waren Ans, Veronica en Eveline. Het is al even geleden, maar ik vergeet jullie nooit meer!

De laatste jaren was ik er steeds minder, maar gelukkig was het op de UU altijd gezellig met alle andere parttime onderzoekers op kamer 007. Dank ook Erik Oudman dat je mij mooi kon voorschetsen wat ik kon verwachten.

In de kliniek van Nieuw Unicum voelde ik mij meteen thuis, en dat had niet alleen met het werk te maken maar vooral ook met het team. Heel afdeling behandelzaken is nauw betrokken bij de cliënten en bij elkaar. Dat is heel bijzonder, en dat ik daar zo prettig mijn plaats in kreeg zorgde dat ik de combinatie met het onderzoek volhield. In het bijzonder de collega's van de 'psychosociale dienst' (Saskia, Helga, Fred, Irene en nu

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Judith: We maken een bijzondere periode mee, ik ben blij dit met jou te kunnen delen. Kom snel terug naar Amsterdam, je hoort hier!

Pama: ik weet hoe trots jullie zijn. Jullie vertrouwen volledig in mijn kunnen, en hebben me altijd gestimuleerd tot zelfstandigheid. Ik sta nu dan wel op eigen benen, maar jullie betrokkenheid blijft heel belangrijk voor mij. Broertjes: ik heb uiteindelijk wel gewonnen als eerste met de doctorsbul, maar ik verwacht nog veel van jullie... en houd van jullie inclusief aanhang en kroost.

Glasjes: wat een familie. Ik kan geen genoeg krijgen van alle Whatsappjes, weekendjes weg, gesprekken aan de keukentafel en meer. Jullie zijn lief.

Jannes, wat kan ik zeggen? Ik ben al heel lang heel graag bij jou, en geloof dat dat niet meer overgaat. Ik heb je lief. Wij delen ons leven, elk met een eigen kijk daarop, beiden met een open nieuwsgierige blik. Laten we ons samen verwonderen over wat er allemaal nog gaat komen.

Het leven is 1 groot experiment. Op naar nieuwe fases in werk en leven!

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Kant N, Postma A, van Zandvoort MJ, Naura IM, Geurts JJG, van den Berg E (under revision). The Cognitive Profile of Advanced Multiple Sclerosis.

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Curriculum vitae

Neeltje Kant werd geboren op 3 november 1982 te Nijmegen.

Zij studeerde Psychologie aan de Universiteit van Utrecht (UU). In 2008 behaalde zij daar zowel haar masterdiploma in de Klinische Neuropsychologie als van de multidisciplinaire researchmaster Neuroscience and Cognition. Tijdens haar studie doorliep zij een klinisch neuropsychologische diagnostiekstage in het Universitair Medisch Centrum Utrecht (UMCU), bij de afdelingen Neurologie en Revalidatiegeneeskunde, onder begeleiding van dr. Martine van Zandvoort en dr. Carla Ruis. Als eerste onderzoeksstage verrichtte zij fMRI onderzoek bij het Rudolf Magnus Instituut voor Neurowetenschappen op de afdeling Volwassenenpsychiatrie van het UMCU , bij dr. Matthijs Vink, naar het beloningssysteem in het brein van patiënten met OCS (obsessieve-compulsiviteitsstoornis). Daarna startte zij bij prof. dr. Albert Postma op de afdeling Psychologische Functieleer van de UU met haar laatste stage, waarbij zij onderzoek deed naar dissociaties tussen spatiële en temporele aspecten van het geheugen. Dit project vormde het begin van een reeks onderzoeken die uiteindelijk de kern vormen van dit proefschrift.

Neeltje begon na haar afstuderen als junior docent en onderzoeker aan de UU, waar zij haar onderzoeksprojecten continueerde. In 2009 kreeg zij tevens een baan als neuropsycholoog bij Nieuw Unicum, te Zandvoort, zorgaanbieder in de lichamelijke gehandicaptenzorg met als focus MS expertise, waar zij 4 dagen per week werkzaam is. Neeltje verricht daar neuropsychologische diagnostiek, en biedt behandeling en begeleiding aan cliënten en naastbetrokkenen bij cognitieve, emotionele en gedragsproblemen. Naast haar klinische werk behield zij een part-time aanstelling als junior onderzoeker aan de UU, wat in 2010 werd omgezet in een promotietraject. Daarvan staan de resultaten in dit proefschrift beschreven. Op het moment van schrijven loopt een subsidieaanvraag om als postdoctoraal onderzoeker te gaan werken in een samenwerkingsverband tussen kliniek (Nieuw Unicum) en wetenschap, vanuit het VUmc MS Centrum te Amsterdam. Daarmee zou Neeltje haar wetenschappelijke en klinische werkzaamheden kunnen blijven combineren. Het is daarbij steeds haar doel om het leven van mensen met hersenletsel te verbeteren.