Neuropsychology
2017, Vol. 31, No. 7, 735–749

0894-4105/17/$12.00 http://dx.doi.org/10.1037/neu0000378

Spontaneous Retrieval Deficits in Amnestic Mild Cognitive Impairment: A Case of Focal Event-Based Prospective Memory

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Objective: Research on early cognitive markers of Alzheimer's disease is primarily focused on retrospective recall (of word lists, pairs of items, stories) and executive functions. However, research shows that people with amnestic mild cognitive impairment (aMCI), who are at a higher risk of developing the disease than healthy controls, are particularly impaired in remembering to do things in the future or prospective memory (PM). The aim of this study was to establish which type of event-based PM is particularly disrupted in aMCI, focal PM, based on spontaneous retrieval, or nonfocal PM that relies on strategic monitoring processes. ***Method:*** Thirty-eight aMCI individuals and 46 age- and education-matched healthy older adults identified the profession of each famous face presented (ongoing task) and, additionally, responded to certain professions (focal PM condition), or to certain physical features of a person presented (nonfocal PM). Only 4 aMCI individuals could not remember PM instructions at the end of the session, and were excluded from analyses. ***Results:*** In comparison with healthy controls, participants with aMCI were significantly impaired in the focal PM task, but not on the nonfocal task. In both groups, monitoring indices were significantly higher in the nonfocal than focal PM condition. ***Conclusions:*** The results fully replicate and extend initial findings of Chi et al. (2014) and McDaniel, Shelton, Breneiser, Moynan, and Balota (2011), showing substantial spontaneous retrieval deficits in PM performance of aMCI individuals. Possible brain mechanisms involved in this deficit are discussed and a novel hypothesis of more generic spontaneous retrieval deficits in aMCI is proposed.

General Scientific Summary
Early identification of individuals at increased risk of developing Alzheimer's disease is important as it can help patients and caregivers to adjust to changes and manage the disease more effectively. Our results indicate that cognitive tasks, based on spontaneous effortless retrieval processes, can be more sensitive to early signs of brain pathology in Alzheimer's disease than the standard tests of episodic memory, and can help clinicians to improve diagnostic accuracy.

Keywords: Alzheimer's disease, amnestic mild cognitive impairment, focal event-based prospective memory, nonfocal event-based prospective memory, early cognitive marker

With increased life expectancy, the number of people diagnosed with Alzheimer's disease (AD) and other forms of dementia is growing steadily, and presents a significant challenge to health care systems and society at large (World Alzheimer Report, 2015, http://www.alz.co.uk/research/world-report-2015). One of the defining symptoms of AD is an impairment in declarative memory. This impairment is associated with several changes in the medial lobe structures such as the tau protein pathology spreading from the perirhinal to the entorhinal cortex and then to the hippocampus (Bobinski et al., 1999; Braak & Braak, 1991; Head, Snyder,

This article was published Online First April 13, 2017.

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This research was supported by a Marie Sklodowska-Curie Intra-European Fellowship within the 7th European Community Framework Programme. We thank all the old age psychiatrists, clinical psychologists, and nurses from EMDASS and SMHT in Hertfordshire for their help in the recruitment process. We are particularly grateful to Amirtha Pasupathy, Shora Shaheen, Jenny Noero, Edward Smith, Marianne Kreutz, Guney Dillioglu, and Heather Condon for their support throughout the study and invaluable help in reaching our recruitment goals.

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Girton, Morris, & Buckner, 2005; Nickl-Jockschat et al., 2012). It is accompanied by the formation of beta-amyloid depositions in several cortical regions, especially in the brain's default network (posterior cingulate cortex, lateral parietal and medial prefrontal regions) that have dense connections with medial temporal lobes (Buckner et al., 2005). Moreover, the pathological process may start years, or even decades before the clinical diagnosis of dementia (Morris, 2005; Sperling et al., 2011). Therefore, researchers and clinicians have been keen to find cognitive markers that can identify older adults at high risk of developing AD. Despite ongoing research, there is uncertainty about the best early cognitive markers of AD (e.g., Gainotti, Quaranta, Vita, & Marra, 2014; Ozer, Young, Champ, & Burke, 2016). In addition, standard test batteries consist of tasks measuring episodic memory of past events (i.e., retrospective memory) and executive functions, and ignore the emerging evidence that it is prospective memory that is particularly impaired in early stages of AD (Van den Berg, Kant, & Postma, 2012).

Prospective memory (PM) is an ability to remember to do something in the future, for example, taking a pill with breakfast (event-based PM) or keeping an appointment at 3:00 p.m. (time-based PM). It is vitally important for successful everyday functioning not only in healthy older adults, but also in other populations including cognitively impaired older adults (Schmitter-Edgecombe, Woo, & Greeley, 2009; Smith, Della Sala, Logie, & Maylor, 2000). In contrast to retrospective memory (e.g., recalling a story when asked), PM tasks involve multiple and distinct cognitive operations that underlie recalling the intended action on one's own initiative while being involved in unrelated ongoing activity (Ellis, 1996; Kliegel, Mackinlay, & Jäger, 2008). It has been suggested that the multifaceted nature of PM tasks may render them more sensitive, in comparison to retrospective memory tasks, to the detection of subtle cognitive deficits in the aging population (Chi et al., 2014). There is indeed evidence to suggest that not only do PM tasks add additional discriminative power to the detection of early stage AD, above and beyond the known psychometric tests of retrospective memory (Duchek, Balota, & Cortese, 2006; McDaniel, Shelton, Breneiser, Moynan, & Balota, 2011), but they may also make an independent contribution, beyond that of retrospective memory, to the prediction of AD in cognitively healthy older adults three years later (Jones, Livner, & Bäckman, 2006). Despite these intriguing results, the research on diagnostic utility of PM is in its initial stage and there is clear need for more systematic and theory-driven investigation.

Moreover, recent research has shifted from studying PM in people with AD to individuals with amnestic Mild Cognitive Impairment (aMCI) to examine whether PM tasks are also useful in detecting signs of cognitive decline in people who do not yet meet the criteria for dementia. aMCI is characterized by the presence, in a nondemented elderly individual, of a memory deficit perceived as a significant decline by the individual involved, or by a family member, and objectively confirmed by scores below the norm on psychometric tests of episodic memory (Petersen, 2004). It is a borderline condition between normal aging and dementia, with aMCI individuals having a much higher risk of progression to dementia of the Alzheimer's type than that expected in age-matched normal people (Petersen, 2004).

A meta-analysis of seven studies on PM in MCI showed statistically significant and large PM deficits in patients with MCI in all the studies irrespective of the type of PM task used (Van den Berg et al., 2012). The findings have been explained by the influential multiprocess theory of PM (McDaniel & Einstein, 2000, 2007), which stipulates that remembering a PM task is a complex process which, depending on the task parameters, may be mediated either by strategic and effortful monitoring processes or by spontaneous retrieval where the intention simply pops into mind at the right moment. Moreover, time-based tasks are generally more difficult to remember as they require self-initiated time-monitoring in the absence of explicit cues, whereas in event-based tasks remembering is facilitated by the target event (e.g., seeing a postbox when intending to post a letter), which may spontaneously bring the intention to mind due to associative links between the target event and intended action. However, not all event-based tasks are retrieved via associative retrieval processes. The theory distinguishes focal and nonfocal event-based PM tasks that lie at the opposite ends of the spontaneous versus strategic continuum. In focal PM tasks, spontaneous retrieval is facilitated by having to process the PM cue as part of the ongoing task and by an overlap between the features of the PM cue and the ongoing activity (e.g., responding to a target word "office" while semantically processing words in the ongoing task). In nonfocal PM tasks, the processing of the ongoing task does not encourage the noticing of the PM cue and successful remembering requires continuous or intermittent strategic monitoring (e.g., responding to a syllable "tor" during the ongoing task requiring semantic processing of words).

Given that strong deficits in PM have been documented in all the studies on aMCI, using time-based as well as focal and nonfocal event-based tasks, there is growing consensus that aMCI disrupts both spontaneous and strategic retrieval processes in PM. However, results of some studies show that PM in aMCI may be particularly impaired in those time-based and nonfocal event-based tasks that require more effortful and strategic monitoring (Blanco-Campal, Coen, Lawlor, Walsh, & Burke, 2009; Karantzoulis, Troyer, & Rich, 2009; Tam & Schmitter-Edgecombe, 2013; Troyer & Murphy, 2007). This has been explained by disrupted abnormalities in the prefrontal cortex, in addition to temporal lobes, found in MCI patients in some structural and functional neuroimaging studies (e.g., see Costa et al., 2010).

In stark contrast to these findings and their interpretation, McDaniel, Shelton, Breneiser, Moynan, and Balota (2011) compared performance in focal and nonfocal event-based PM tasks and found that in comparison with healthy controls, participants with very mild AD (the global score of .05 on the Clinical Dementia Rating Scale) were disproportionately more impaired in an easy focal event-based task, mediated by spontaneous retrieval processes, than in a nonfocal task requiring more effortful and strategic monitoring. Chi et al. (2014) extended these novel findings to people with aMCI. As in McDaniel et al.'s (2011) study, participants were engaged in a category decision task, in which they indicated whether a word on the left belonged to the category on the right. The PM task involved remembering to press a key when they saw the word "tulip" or the syllable "rad" (the focal and nonfocal PM conditions, respectively). Results showed that aMCI participants were significantly impaired on the focal, but not on the

nonfocal PM task in comparison with healthy controls.[1] Chi et al. (2014) concluded that aMCI primarily penalized spontaneous retrieval and did not further compromise strategic monitoring processes over that produced by normal aging.

McDaniel et al. (2011) explained these counterintuitive findings by Moscovitch's (1992, 1994) component process model of memory, which suggests that the function of hippocampus and related structures in the medial temporal lobe is to automatically encode events as long as they are fully attended, and in the presence of the right cue, to reactivate the associated memory trace in an obligatory fashion, resulting in spontaneous, effortless recall. Hence, the subtle changes in hippocampus and medial temporal lobes in early stages of AD would be particularly sensitive to focal event-based tasks that are based on such reflexive associative retrieval processes that automatically bring the intention representation to mind in response to a focal cue. In contrast, people with mild AD could still deploy some strategic monitoring in more difficult nonfocal PM tasks, because of their relatively preserved prefrontal cortex that becomes compromised at a later stage of the disease (Braak & Braak, 1991).

However, several other studies have failed to replicate initial findings of McDaniel et al. (2011) and Chi et al. (2014). Lee, Shelton, Scullin, and McDaniel (2016) found that PM was equally disrupted in focal and nonfocal tasks in very mild AD. This could be due to their small sample size, as many participants with AD could not remember PM instructions at the end of the ongoing task, and were excluded from the analysis. Tam and Schmitter-Edgecombe (2013) compared participants with aMCI and healthy controls only on a nonfocal event-based task, requiring strategic retrieval, and found a significant impairment in the aMCI group. In addition, when Blanco-Campal et al. (2009) compared the discriminatory power of focal and nonfocal PM tasks to detect aMCI from healthy controls, they found that although both PM tasks demonstrated reasonable sensitivity and specificity, it was the nonfocal PM performance that had higher discriminative efficacy and was superior to all the retrospective memory tests.

In light of these contradictory findings, the validity of the idea that it is focal PM that is particularly disrupted in very early stages of AD is far from clear, and needs more systematic investigation. Consequently, the main aim of the present investigation was to provide a definitive test of disproportionate impairment of focal PM in aMCI, by using a novel PM task, and addressing some of the methodological limitations of previous studies.

First, as suggested by Costa, Caltagirone, and Carlesimo (2011), inconsistent findings concerning the nature of cognitive processes underlying PM deficits in MCI may be due to variations in how MCI was classified, and, in some studies, the inclusion of different MCI subtypes within the same test group (e.g., individuals with multiple domain aMCI, who show deficits in both the memory and executive function tasks, or individuals with dysexecutive MCI who show deficits in executive tests only). Therefore, in addition to having a clinical diagnosis of MCI, we administered a neuropsychological test battery to ensure that our MCI participants met the criteria for single domain aMCI (Petersen, 2004; Winblad et al., 2004).

Second, in contrast to all previous studies that manipulated PM cue focality in patients with aMCI and healthy controls using a within-subjects design, in the present study a between-subjects design was used for the first time. Although both designs have their advantages and disadvantages (Field, 2013; Greenwald, 1976), a between-subjects design was specifically chosen to avoid possible carry-over effects, that is, transferring cognitive operations for performing a PM task (e.g., employing vs. not employing strategic monitoring) from one condition to the other (from the focal to the nonfocal condition and vice versa).

Third, in addition to problems with recruiting sufficiently large clinical samples, studies on PM in MCI need to factor in potential loss of MCI participants, which can be substantial, due to their failure to retrospectively recall PM instructions at the end of the task. To ensure sufficient power, we performed the a priori power analysis on GPOWER 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007). The effect size calculation was based on the PM cue focality by group interaction reported by McDaniel et al. (2011) ($f = .37$). With an alpha level of .05 and the minimum power of .90, 80 participants were necessary to find a statistically significant effect in the model.[2] We tested 94 participants, to account for a loss of participants due to the retrospective memory failure or other reasons.

Fourth, when designing the PM task for cognitively impaired older adults, it is important to engage them in ongoing tasks with fairly large number of PM targets (to increase reliability) without exhausting their already diminished cognitive resources or boring them with the repetitive nature of the task (e.g., simple decisions for hundreds of trials). Inspired by a famous faces task by Maylor (1993; see also Rendell, McDaniel, Forbes, & Einstein, 2007), we developed a new highly engaging computerized ongoing task, resembling a TV quiz, in which participants had to recognize the profession of each famous face (person), presented on a computer screen, by choosing one out of four professions provided.

Fifth, in all three previous studies that compared focal and nonfocal PM in healthy controls and patients with aMCI or very mild AD, different PM targets were used in the focal and nonfocal conditions.[3] In the present study, the cue focality was manipulated by asking participants to touch a triangle in the upper right hand corner if they saw a picture of a politician or royalty (the focal condition), or a picture of a person wearing glasses or having a

[1] Although aMCI is considered roughly equivalent to the global score of .05 on the Clinical Dementia Rating (CDR) Scale, they are not totally overlapping diagnostic categories (Petersen, 2004). In fact, there is a lack of consensus on this issue with some studies showing that the CDR score of .05 taps into more severe end of MCI diagnosis (Woolf et al., 2016), while others have shown that it may be more sensitive to cognitive and functional changes present in pre-MCI individuals (e.g., Saxton et al., 2009). It is therefore essential that the disproportionate impairment on focal PM compared with nonfocal PM is demonstrated in both individuals with aMCI and those with the CDR score of .05.

[2] If we adopted a minimum power of .80, normally used by researchers following Cohen's (1988) recommendations, we would need only 60 participants. We used a more conservative criterion of .90 because our design was different from that of McDaniel et al. (2011): cue focality was a within-subjects factor in their study and a between-subjects factor in our study.

[3] In studies by McDaniel et al. (2011) and Lee et al. (2016), there was a partial overlap for only one, out of three, targets presented. For example, the focal PM target "raspberry," occurring three times, and the nonfocal syllable "ras" occurring in words "raspberry," "harassment," and "grasshopper" involved partial overlap between focal and nonfocal conditions for the word "raspberry." However, the word raspberry and the syllable "ras" are not identical as stand-alone items. Moreover, the remaining two targets in each condition were completely different.

hand visible in the photograph (the nonfocal condition). Thus, cues in the focal and nonfocal conditions differed in their relevance to the features processed to recognize the profession: being a politician or royalty was directly relevant to the ongoing task, whereas the presence of glasses or a hand was not. Importantly, as all four politicians were wearing glasses and all four royal persons had their hand visible, the same eight pictures served as the PM cues in the focal and nonfocal conditions.

Finally, in the present study, we calibrated the speed at which pictures were presented in the ongoing task for each participant individually. In research so far, the speed of presentation was the same for all participants (Tam & Schmitter-Edgecombe, 2013) or longer in the aMCI than in the control group (Blanco-Campal et al., 2009) to control for processing speed deficits in MCI. However, individual differences in cognitive abilities, including those in processing speed, substantially increase in old age (Glisky, 2007; McDaniel, Einstein, & Jacoby, 2008), and especially in individuals with MCI (Haworth et al., 2016). This means that researchers need to control not only for differences in processing speed between aMCI and control participants, but also individual differences within the groups of aMCI and control participants. Therefore, the speed of presentation in our ongoing task was tailored to the time the participant required in a calibration phase that preceded the main ongoing task. In addition, we manipulated the presentation speed within subjects, by having half of the photographs presented at the speed that the participant required to recognize a profession in the calibration phase (standard speed) and the other half being presented at a faster rate.

The main hypothesis of the present study was that, compared to healthy older controls, aMCI individuals would be more severely impaired on focal PM tasks, based on spontaneous retrieval, than on nonfocal PM tasks that require strategic monitoring. The prediction of this group by PM cue focality interaction was based on initial findings by McDaniel et al. (2011) and Chi et al. (2014) on participants with very mild AD and aMCI, respectively. We also manipulated the ongoing task demands (standard vs. fast presentation rate). Although this manipulation was exploratory, we wanted to examine if it influenced a pattern or size of differences between aMCI individuals and controls. For example, no significant group differences were found in nonfocal PM tasks by McDaniel et al. (2011) and Chi et al. (2014), while several other studies have found significant group differences in such tasks (e.g., Tam & Schmitter-Edgecombe, 2013). It is therefore possible that significant differences between aMCI participants and controls in the nonfocal condition would emerge only for a more demanding ongoing task, with fast presentation rate.

The second set of hypotheses was based on the multiprocess theory of PM (McDaniel & Einstein, 2000, 2007), and concerned the role of strategic monitoring in PM performance of aMCI individuals and healthy controls. The theory assumes that strategic monitoring is necessary for nonfocal PM, whereas it does not underlie PM performance in focal PM. In the latter, it may still appear in some participants with a tendency to monitor, but it is not crucial to perform well (Einstein & McDaniel, 2010; Einstein et al., 2005). Hence, it was predicted that monitoring indices would (a) be higher in the nonfocal than the focal PM task, and (b) be positively related to PM scores only in the nonfocal PM task. As our core assumption was that aMCI primarily disrupts spontaneous retrieval without significantly affecting strategic monitoring over that produced by normal aging, we expected the above pattern in both the aMCI and control participants with no group differences in the monitoring frequency.

The most often used method of analyzing monitoring in PM involves comparing reaction times (RTs) in the ongoing tasks between different PM and control (no PM task) conditions, with costs of monitoring measured as slower RTs in PM conditions (e.g., Chi et al., 2014; McDaniel, Shelton, Breneiser, Moynan, & Balota, 2011). We adopted a different approach for two reasons. First, for our ongoing task, RT was not available as the time for an answer was set (after calibrating it for each participant) and manipulated within subjects (standard vs. fast presentation rate). Second, a recent study by Heathcote, Loft, and Remington (2015), using formal diffusion and linear ballistic accumulator modeling of RT data, has called into question the assumption that the cost actually measures monitoring. Therefore, to assess monitoring, we compared the focal and nonfocal PM conditions on self-rated rehearsal and the frequency of overt rehearsal. The first measure has already been used many times to analyze monitoring in PM (e.g., Maylor, 1998; Tam & Schmitter-Edgecombe, 2013), whereas the second measure, to our best knowledge, was adopted for the first time. During piloting, we noticed that both aMCI and control participants tended to think aloud and make comments about how they were performing the PM task. Therefore, we recorded the frequency of those comments that implied rehearsing the PM task while being engaged in the ongoing task.

Method

Design

The design was a 2 × 2 × 2 mixed-factor design, with Group (aMCI vs. healthy controls) and PM task (focal vs. nonfocal) as between-subjects factors and presentation speed (standard vs. fast) as a within-subjects factor.

Participants

A total of 48 healthy older adults and 46 aMCI participants were recruited and randomly assigned to the focal and the nonfocal PM cue conditions. The study was approved by the National Research Ethics Service Committee-Cambridgeshire and Hertfordshire. For all participants, exclusion criteria included: (a) head/brain injuries, (b) history of cerebrovascular disease, (c) history of alcohol or substance dependence, (d) medical, neurological, or psychiatric disorders resulting in cognitive dysfunctions, (e) age less than 60 years. Fluency in English and adequate vision and hearing were also required. Exclusion criteria were assessed in the initial phone screening. Participants who passed the screening, completed a battery of experimental and standardized neuropsychological tests, in two sessions one week apart.

MCI participants. The MCI participants were referred from Specialist Mental Health Teams for Older People and Early Memory Diagnosis and Support Services (memory clinics). They all had MCI diagnosis via multidisciplinary diagnostic consensus (i.e., neurological, psychiatric, radiological, neuropsychological, and functional assessment). The majority (87%) were diagnosed within a couple of weeks before the study. The clinical diagnosis was confirmed using the inclusion criteria that satisfied the diagnostic

criteria of aMCI (Petersen, 2004; Winblad et al., 2004): (a) presence of a subjective memory complaint (i.e., sought professional assessment due to concerns about memory decline); (b) objective memory impairment evidenced by a score at or below 1.5 *SD* of the mean of age-matched peers on at least one test of the neuropsychological screening battery assessing episodic memory (see the Neuropsychological Evaluation section); (c) not meeting the *Diagnostic and Statistical Manual of Mental Disorders'* (*DSM–5*) criteria for dementia (American Psychiatric Association, 2013); (d) preserved general cognitive function as confirmed by a normal score on the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975; normality cut-off score: 24; Measso et al., 1993); (e) maintained activities of daily living or slight impairment in instrumental activities of daily living, as confirmed by no more than one item showing deterioration in the Lawton Instrumental Activities of Daily Living scale (IADL; Lawton & Brody, 1969); (f) absence of severe depression, as confirmed by a score below 20 on the Geriatric Depression Scale 30 (GDS30; Yesavage et al., 1983).

Five aMCI participants (three from the focal and two from the nonfocal conditions) did not meet the criteria for a single domain aMCI (with episodic memory deficits only). They all scored 1.5 standard deviations or more below age-appropriate means on at least one of the tests of short-term memory (STM), attention and executive functions (see the Neuropsychological Evaluation section below), and therefore satisfied the criteria of multiple domain aMCI (Petersen, 2004). Although at a group level, single domain aMCI participants scored reliably lower than healthy controls on almost all of these measures, none of them scored at 1.5 standard deviations or below unlike the five participants with multiple domain aMCI. To have a homogeneous sample of single domain aMCI, we excluded these five participants from the sample.

Furthermore, two aMCI participants withdrew after the first session and one participant who was unable to concentrate/follow task instructions, was excluded after the first session. Finally, four aMCI participants had to be dropped because they were unable to recall or recognize the PM instructions when queried at the end of the ongoing task (see the Procedure section and Footnote 4). The final sample therefore consisted of 34 participants with single domain aMCI, with 17 participants in each of the two conditions.

Healthy controls (HC). HC were recruited through advertisements in the local community and lunch and social clubs for older adults as well as a database of the older adult volunteers maintained by the second author. Inclusion criteria for the HC group were: (a) absence of a subjective memory complaint (i.e., had not sought professional assessment due to concerns about memory performance); (b) a score within or above 1.5 *SD* of the mean of age-matched peers on each test of the neuropsychological screening battery assessing episodic memory; (c) a score ≥27 on the MMSE; (d) no impairment in instrumental activities of daily living, as confirmed by a maximum score on the Lawton IADL; (e) absence of severe depression, as confirmed by a score of below 20 on the GDS30.

All HC were able to recall or recognize the PM instructions at the end of the task and only two participants withdrew between the first and the second sessions, resulting in a sample of 46 participants (24 in the focal and 22 in the nonfocal condition). Table 1 shows demographic details of the final samples of HC and single domain aMCI. A series of 2 Group (aMCI vs. HC) × 2 PM cue type (focal vs. nonfocal) between subjects ANOVAs were conducted on these variables (for gender, chi square tests were used). No significant main or interaction effects were found for any of the demographic variables, except for the main effect of group for MMSE scores, which were significantly higher in HC than in aMCI individuals ($p < .001$; $\eta_p^2 = .35$).

Measures

Neuropsychological evaluation. Standardized tests were administered to all participants to assess episodic memory, STM as well as attention and executive functions. The episodic memory tests included the Hopkins Verbal Learning Test– Revised (HVLT-R; Brandt & Benedict, 2001), consisting of three immediate recall and one delayed recall tests, and several tests from the Wechsler Memory Scale–3rd edition (Wechsler et al., 1998): logical memory subtest (immediate recall and delayed recall); verbal paired associates (immediate recall and delayed recall); two tests of STM (digit span forward and digit span backward). The attention and executive function tests included verbal fluency test: letter fluency (Spreen & Strauss, 1998), and category fluency (Rosen,

Table 1
Demographic Characteristics as a Function of Group (aMCI vs. Healthy Controls) and Prospective Memory Cue Condition (Focal vs. Nonfocal)

	aMCI		Healthy controls	
Variable	Focal cue (n = 17)	Nonfocal cue (n = 17)	Focal cue (n = 24)	Nonfocal cue (n = 22)
Sex	59% women	65% women	58% women	64% women
Age	79.82 (6.67)	77.71 (6.61)	76.38 (8.45)	76.41 (7.53)
Education (years)	11.53 (3.00)	11.41 (2.90)	12.63 (2.96)	12.46 (2.81)
NART	35.63 (5.90)	37.36 (9.27)	39.22 (4.60)	35.62 (7.55)
Mood	6.82 (5.72)	7.35 (5.18)	7.21 (4.79)	5.14 (4.98)
Health at present	3.53 (1.13)	3.53 (1.33)	3.71 (.81)	3.91 (.77)
Health vs. peers	3.47 (.94)	3.77 (1.09)	3.83 (.96)	3.95 (.59)
MMSE	27.59 (1.77)	27.41 (1.87)	29.54 (.78)	29.32 (.89)

Note. aMCI = amnestic Mild Cognitive Impairment; NART = National Adult Reading Test; Mood = Geriatric Depression Scale 30; MMSE = Mini-Mental State Examination; Health at present (1 = poor, 5 = excellent); Health compared with peers (1 = worse, 3 = same, 5 = significantly better).

1980), and the Trail Making Test (TMT): Part A and B (Reitan, 1958).

Table 2 shows mean scores on tests of neuropsychological battery as a function of group (aMCI vs. HC) and effect sizes for group differences. These means were entered into a series of 2 (Group) × 2 (PM cue type) between subjects ANOVAs. The main effect of group was significant for all the tests, except for the digit span forward and backward, with HC group outperforming the aMCI group. In line with the criteria for single domain aMCI classification, the effect sizes for episodic memory tests were markedly higher than for the tests measuring attention and executive functions. The main effect of PM cue condition was not significant and did not interact with group for any of the tests from the battery.

Experimental Materials

The ongoing task consisted of 180 color photographs of actors, singers, sportspersons, TV news presenters, TV show hosts, chefs, comedians, film directors, writers, politicians, and royalty. Photographs were piloted on a sample of 30 healthy older adults to ensure that people in the photographs were familiar to the older population. The pilot also aimed to select PM target items, that is, British politicians and members of the royal family, who would all be easily recognized by older adults. This would ensure that a lack of PM response to these photographs was due to a PM failure rather than inability to recognize a politician or a royal person. A final set of photographs included four members of the royal family (the Duchess of Cambridge, Prince Harry, the Prince of Wales, the Duke of Edinburgh) and four politicians (Alistair Darling, John Major, Tony Blair, and Boris Johnson).

Stimulus presentation and the response collection were controlled by Inquisit 4.06 software running on a 14" foldable notebook with a touch screen. Photographs measured on average 15° (height) × 13° (width) (12.5 × 9.0 cm) at a viewing distance of 60 cm and were presented on a white background on the left half of the screen. They were viewed in a random order and the order was the same for each participant. Photographs were divided into six blocks of 30, with each block including either one or two target photographs, that is, photos of politicians wearing glasses and royal persons with a hand visible in a photograph. The target photographs were in set positions in each block—Block 1: 25 (royalty); Block 2: 15 (politician); Block 3: eight (politician) and 28 (royalty); Block 4: 25 (royalty); Block 5: 18 (politician); and Block 6: nine (royalty) and 29 (politician).

Each photograph was presented with a list of four professions to choose from (in black 50-point Verdana font) and four small triangles (Greek Capital letter delta in 35-point Symbol font), one triangle in each corner of the computer screen. A set of four professions was different with each photograph. The limitations of our software in displaying a photo with multiple response options, and having the additional PM task, did not allow for full randomization of the content of four response options. Therefore, we chose an approximation to random assignment of four professions to each photograph. For each picture of a famous person, we randomly assigned one of the four professions that were never represented by people in the photographs (lawyer, scientist, fashion designer, and businessperson). For the next two options we randomly assigned two professions, which were not the correct answers. The fourth choice was the correct answer. The correct answer was placed in each of the four positions (a, b, c, d) with the same frequency. We took care that two professions representing wrong answers appeared with the same frequency, with some exceptions though. To ensure that sets of professions to choose from would not remind participants about PM task during the ongoing task, "politician" and "royalty" never appeared as an option except for the photographs that presented a politician or

Table 2
Mean Scores on Neuropsychological Test Battery in Participants With aMCI and Healthy Controls

Test	aMCI (n = 34)	HC (n = 46)	η_p^2
Episodic memory			
WMS logical memory: immediate recall	21.71 (8.92)***	42.80 (11.05)	.52
WMS logical memory: delayed recall	7.85 (8.03)***	25.52 (7.51)	.57
WMS verbal paired associates: immediate recall	6.50 (6.31)***	16.85 (7.14)	.37
WMS verbal paired associates: delayed recall	1.94 (1.97)***	5.44 (2.42)	.38
HVLT: immediate recall 1	3.65 (1.59)***	6.58 (1.63)	.45
HVLT: immediate recall 2	5.21 (1.61)***	8.53 (1.82)	.48
HVLT: immediate recall 3	6.27 (1.46)***	9.51 (1.77)	.50
HVLT: delayed recall	2.77 (3.11)***	8.49 (2.60)	.51
Short-term memory			
WMS digit span: Forward	10.18 (2.24)	10.33 (2.55)	.001
WMS digit span: Backward	6.71 (2.25)	7.44 (2.38)	.02
Attention and executive functions			
Verbal fluency: Letters	33.65 (13.37)*	41.07 (13.42)	.07
Verbal fluency: Category	11.85 (4.43)***	17.76 (5.56)	.25
Trail Making Test—Part A	45.07 (11.55)**	36.48 (11.23)	.13
Trail Making Test—Part B	124.54 (57.06)***	81.02 (33.54)	.19

Note. aMCI = amnestic Mild Cognitive Impairment; HC = healthy controls; HVLT = Hopkins Verbal Learning Test; WMS = Wechsler Memory Test. For each test, a high score indicates a better performance with the exception of scores referring to time used to complete the Trail Making Test (A and B). Differences between aMCI and HC are indicated by * $p < .05$. ** $p < .01$. *** $p < .001$.

royalty. Similarly to the target professions, "comedian" never appeared as an option except for the photographs that presented comedians.

For half the blocks, slides with photographs and professions to choose from, were presented at a speed comfortable to the participant, that is, with the speed that the participant required to recognize the face in the calibration phase (see the Procedure section). The mean presentation speed for aMCI individuals (M = 7.97; SD = 2.12; range 5–13 s), was reliably longer than for HC (M = 7.07; SD = 1.67; range 5–12 s), $t(78) = 2.14$, $d = .47$. For the other half of the blocks, slides were presented at fast speed. This was achieved by subtracting one third of the mean time that the participant needed to recognize faces in the calibration phase. A reminder "Choose now!" appeared on the screen 3,000 ms before the end of each slide. The photograph remained on the screen for the duration of the trial, irrespective of how quickly the profession was recognized. The standard and fast presentation blocks alternated with half the participants beginning the ongoing task with a standard presentation block and the other half with a fast presentation block.

Procedure

Participants were tested individually, predominantly by the first author at the participant's home. At the beginning of Session 1, participants completed the consent form, demographic items and health ratings. All instructions for the PM task and the ongoing task (recognizing professions) were presented on the computer screen, and additionally the experimenter repeated the main points. The participants were told that they would be shown 180 photographs of famous people, one at a time, and should choose the famous person's profession from a list of professions provided on the screen by touching the right profession. Participants were then presented with five practice photographs to familiarize them with the procedure. We then calibrated the time of presentation for each participant individually. Participants were told that we would first measure how much time they needed to recognize professions from a set of 25 faces. Participant's mean RT, averaged across 25 photographs, was later used in the six blocks of the ongoing task.

After this, the PM instructions were introduced. In the focal PM cue condition, the following instructions were given:

> Although our main interest lies in your ability to recognize people's professions, we are also interested in your attention to detail, in particular, how good you are at noticing people with certain professions. Therefore, if at any point during the presentation, you see a picture of a politician or royalty, we would like you to touch a triangle in the upper right hand corner of the computer screen.

Instructions for the nonfocal PM cue condition specified that:

> Although our main interest lies in your ability to recognize people's professions, we are also interested in your attention to detail, in particular, how good you are at noticing certain characteristics or features of people presented on the screen. Therefore, if at any point during the presentation, you see a picture of a person wearing glasses or a person whose hand is visible in the photograph, we would like you to touch a triangle in the upper right hand corner of the computer screen.

After presenting the PM instructions on the screen, with the experimenter repeating the main points, a practice slide was presented which included: (a) an empty space for a photograph, (b) a list of four professions with a politician among them, and (c) a triangle in each corner. The experimenter then showed the participant what they should do if they saw a politician (focal PM cue condition) or someone wearing glasses (nonfocal PM cue condition) (i.e., she touched the triangle). Finally, participants were asked to repeat, in their own words, what they would be doing on the computer altogether (an ongoing plus a PM task), hence the PM instructions were repeated at least three times. If something was unclear or participants did not remember part of the instructions, the instructions were repeated again. This phase ended only when participants were able to say the instructions for the ongoing and the PM tasks in their own words. Verbal fluency tests (letter and category), lasting about 8 min, were then administered. This was followed by the ongoing task with PM target photographs. At the beginning of each block (from Block 2), participants were told whether they would have a little more or a little less time to recognize the face than in the previous block.

During the ongoing task, the experimenter made a note every time the participant mentioned the PM task. These overt rehearsals involved participants talking to themselves (e.g., "I need to remember about politicians and royalty," "I have not seen any glasses or hands," "Where are politicians and royalty?," "I still need to do glasses and hands").

At the end of the ongoing task, participants' retrospective knowledge of PM instructions was tested with a following question: "Was there anything else you were asked to do on the computer in addition to recognizing professions"? Participants who did not describe the PM task, were given a vague prompt: "Was there anything else you were asked to do if you saw a particular photo"? If participants still did not recall the instructions, they were given a recognition test for PM cues: "I asked you to respond when you saw particular photos. Could you recognize from this list which photographs you were asked to respond to?" The experimenter continued by saying: "What were you asked to do if you saw these photographs?" If participants did not recall the intended action, they were given a recognition test for the intended action: "Which of the following things you were asked to do?"

Next, to assess self-reported monitoring for PM cues, participants were asked whether, while recognizing professions, they thought about the PM task (touching a triangle) (a) only when it was time to touch a triangle, or (b) at some other times as well. If they chose the second option, they were given a 7-point scale (from 1 = *not at all* to 7 = *all the time*) to rate how often they thought about touching a triangle while recognizing professions.

Participants were also asked if they had noticed anything else about the PM targets to assess if participants had noticed that all the politicians were wearing glasses and all the royalties had a hand visible in the picture. No participant reported noticing this. Finally, participants completed the Geriatric Depression Scale 30. The neuropsychological test battery was completed in Session 2. Each session lasted about 2 hr.

Results

For all statistical tests, reported below, the rejection level was set at .05 (unless otherwise specified). The effect size was measured by partial eta squared (η_p^2) with small, medium, and large effects defined as .01, .06, and .16, respectively (Cohen, 1988).

Ongoing Task Accuracy (Recognizing Professions)

The proportion of correctly recognized professions of famous people, in the standard and fast presentation blocks were entered into a 2 group (aMCI vs. HC) × 2 type of PM cue (focal vs. nonfocal) × 2 presentation speed (standard vs. fast) mixed analysis of variance (ANOVA), with presentation speed as the within-subjects variable. This resulted in the main effect of group, $F(1, 76) = 7.34$, $\eta_p^2 = .09$, reflecting superior performance in the HC group ($M = .66$, $SD = .11$) compared with aMCI group ($M = .59$, $SD = .10$). There was also a main effect of presentation speed, $F(1, 76) = 90.84$, $\eta_p^2 = .55$, with more professions correctly recognized in blocks presented with standard ($M = .67$, $SD = .11$) than fast speed ($M = .59$, $SD = .12$). No other effects were significant (all $ps > .09$). There were no significant correlations between the ongoing task performance and PM scores in either HC or aMCI individuals ($ps > .13$).

PM Performance

As indicated in the method section, only four aMCI participants could not remember retrospectively the PM instructions at the end of the ongoing task.[4] We did not exclude from the analyses one HC and three aMCI participants who remembered the intended action, but only one, out of the two, target cues. Their PM score was based on one PM target (which occurred twice in the standard and twice in the fast presentation blocks). In the focal condition, PM response depended on successful recognition of a target photograph as a politician or royalty. All but three aMCI participants correctly identified the professions of all PM target pictures of politicians and royalty (irrespective of whether they made a PM response or not). Out of those three aMCI participants, two participants did not correctly identify only one of the politicians (which means we still had seven valid probes), and one participant did not recognize one of the politicians and one of the royalty (resulting in six valid probes). Hence, their PM scores were based on sufficient number of valid PM trials with correctly recognized politicians or royalty.

The mean proportions of correct PM responses, out of four targets in the standard and fast blocks, were entered into a 2 (group) × 2 (PM cue condition) × 2 (presentation speed) mixed ANOVA. Unlike the results on the ongoing task accuracy (see above), the main effect of presentation speed was not significant and did not interact with other variables ($ps \geq .09$). As expected, PM scores were higher for the focal than for the nonfocal task, $F(1, 76) = 18.52$, $\eta_p^2 = .20$, and aMCI participants demonstrated significantly worse PM than HCs, $F(1, 76) = 18.45$, $\eta_p^2 = .20$. However, these main effects were qualified by a significant group by PM cue interaction, $F(1, 76) = 3.99$, $p = .049$, $\eta_p^2 = .05$ (see Figure 1). As predicted, aMCI participants were significantly impaired ($M = .46$, $SD = .41$) in comparison with HC ($M = .90$, $SD = .23$) in the focal PM task, $F(1, 76) = 20.18$, $\eta_p^2 = .21$, but not in the nonfocal PM task ($M_1 = 0.30$, $SD = 0.32$ and $M_2 = 0.47$, $SD = 0.28$), $F(1, 76) = 2.59$, $p = .11$, $\eta_p^2 = .03$. Alternatively, PM scores were higher for the focal than for the nonfocal task in the HC group, $F(1, 76) = 23.34$, $\eta_p^2 = .24$, but not in the aMCI group, $F(1, 76) = 2.31$, $p = .13$, $\eta_p^2 = .03$.

Next, we examined changes in PM scores from the first half of the ongoing task to the second half (with three blocks of 90 pictures each). The multiprocess theory of PM would predict no significant changes in the focal PM cue condition (as spontaneous retrieval processes do not tax attentional resources), but significant impairment in the second half of the nonfocal task, as effortful monitoring would be difficult to sustain throughout the task. Therefore, mean proportions of correct PM responses were entered into a 2 (group) × 2 (PM cue) × 2 (ongoing task half) mixed ANOVA with the repeated measures on the last factor. In addition to the effects reported in the previous analysis, there was a main effect of ongoing task, $F(1, 76) = 5.70$, $\eta_p^2 = .07$, reflecting superior PM performance in the first rather than second half of the ongoing task. However, this main effect was qualified by a significant interaction with the type of PM task, $F(1, 76) = 8.97$, $\eta_p^2 = .11$ (see Figure 2). As expected, PM performance was significantly worse in the second half of the ongoing task ($M = 0.31$, $SD = 0.36$) than in the first half ($M = 0.47$, $SD = 0.33$) in the nonfocal PM cue condition, $F(1, 76) = 14.23$, $\eta_p^2 = .16$, but no significant differences were observed in the focal PM cue condition between the first half ($M = 0.71$, $SD = 0.38$) and the second half ($M = 0.73$, $SD = 0.40$) of the ongoing task ($F < 1$). None of the other interactions involving the ongoing task was significant ($ps > .37$).

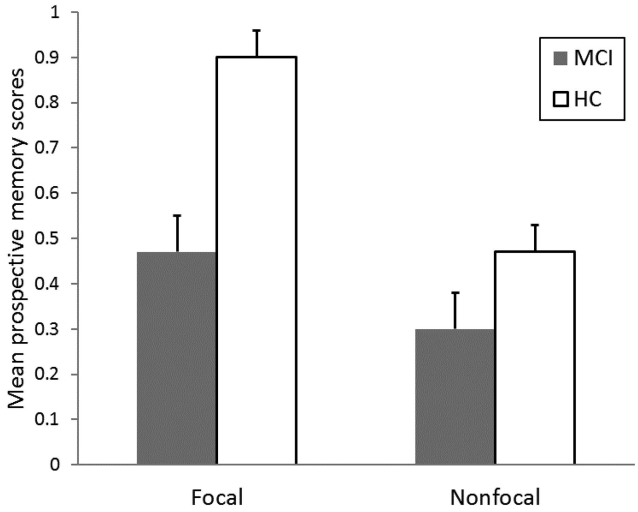

Figure 1. Mean prospective memory scores (with standard errors of the mean) as a function of group (aMCI vs. Healthy Controls) and prospective memory cue condition (focal vs. nonfocal).

Monitoring for PM Cues

Self-rated and overt rehearsals were significantly correlated for both MCI individuals ($r = .66$) and HC ($r = .35$). For nonfocal condition, PM performance significantly correlated with self-reports of monitoring in the entire sample, $r = .33$. There was no relationship between monitoring and PM performance in the focal-condition ($ps > .33$).

[4] One aMCI participant could recognize neither the intended action (touching a triangle) nor the two PM cues, another participant recognized the intended action but neither of the cues, while the remaining two participants recognized one of the cues but neither the intended action nor the other cue.

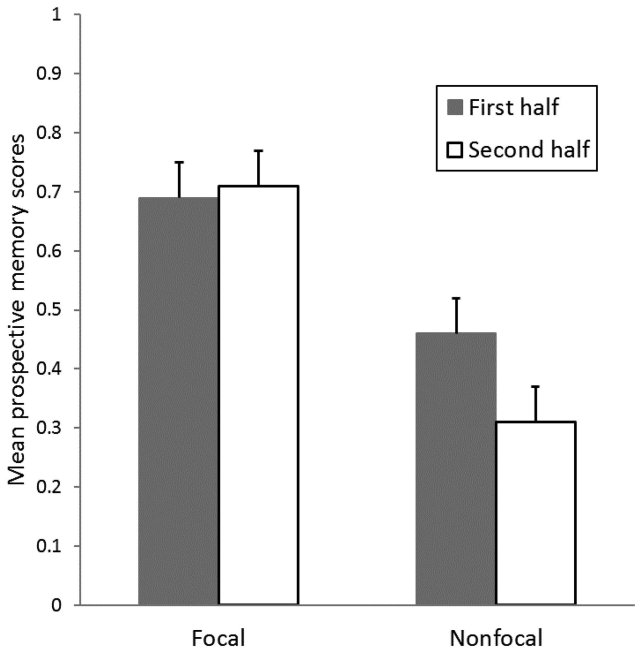

Figure 2. Mean prospective memory scores (with standard errors of the mean) as a function of ongoing task half (first vs. second) and prospective memory cue (focal vs. nonfocal).

To examine whether monitoring frequency differed between PM cue conditions as the multiprocess theory predicts, mean frequencies of self-rated rehearsals were entered into a 2 (group) × 2 (PM cue) factorial ANOVA. As expected, there was a main effect of PM cue type, $F(1, 76) = 8.88$, $\eta_p^2 = .11$, reflecting more frequent rehearsal in the nonfocal ($M = 2.49$, $SD = 1.81$) than focal PM cue condition ($M = 1.42$, $SD = 1.16$). The main effect of group (aMCI vs. HC) was not significant and did not interact with PM cue condition ($ps > .16$).

To examine whether overt rehearsals also differed between PM cue conditions, and whether frequency of overt rehearsals mimicked the pattern of PM performance in the first and second half of the ongoing task for the nonfocal condition, mean numbers of overt rehearsals were entered into a 2 (group) × 2 (PM cue) × 2 (ongoing task half) mixed ANOVA with the repeated measures on the last factor. There was a main effect of PM cue condition, $F(1, 76) = 10.27$, $\eta_p^2 = .12$, reflecting more frequent overt rehearsals in the nonfocal than focal PM cue condition. There was also a main effect of ongoing task, $F(1, 76) = 11.83$, $\eta_p^2 = .14$, with more frequent overt rehearsals in the first than second half of the ongoing task. However, these main effects were qualified by a PM cue by ongoing task interaction, $F(1, 76) = 5.07$, $\eta_p^2 = .06$. As expected, overt rehearsals were less frequent in the second half of the ongoing task ($M = 0.26$, $SD = 0.75$) than in the first half ($M = 0.85$, $SD = 1.50$) in the nonfocal PM cue condition, $F(1, 76) = 15.90$, $\eta_p^2 = .17$, but no significant differences were observed in the focal PM cue condition between the first half ($M = 0.15$, $SD = 0.42$) and the second half ($M = 0.02$, $SD = 0.16$) of the ongoing task ($F < 1$; see Figure 3). The main effect of group (aMCI vs. HC) was not significant and did not interact with other variables ($ps \geq .09$).[5]

Discussion

There is growing evidence to show that performance on PM tasks is significantly impaired in people with very mild AD and aMCI (Van den Berg et al., 2012). However, it is not clear which specific type of PM is particularly disrupted in people with aMCI and can hence serve as an early cognitive marker of the AD. Several studies have shown that it is effortful and resource demanding time and nonfocal event-based tasks that are particularly disrupted at initial stages of the disease. In contrast, McDaniel et al. (2011) and Chi et al. (2014) found that it was the focal (spontaneous) PM task that was significantly more impaired in patients with very mild AD and aMCI than in healthy controls, while group differences on the resource demanding (strategic) nonfocal PM task were not significant.

This is a counterintuitive finding, because the opposite pattern is observed in normal aging whereby healthy older adults perform significantly worse than younger adults in nonfocal PM tasks, but age differences in focal tasks are either absent or small (see Kliegel, Jäger, & Phillips, 2008 for meta-analysis). Therefore, the primary goal of the present study was to provide a definitive test of the disproportionate disruption of focal PM in aMCI, by comparing a group of single domain aMCI individuals with matched healthy older controls and using improved methodology (e.g., between subjects design, the engaging ongoing task with pictorial material and calibrating the difficulty of the ongoing task within participants). The changes in the method were essential for demonstrating the generalizability of the PM cue focality by aMCI status interaction, using other materials and manipulations.

The results of the present study fully replicated and extended initial findings of McDaniel et al. (2011) and Chi et al. (2014). First, in line with predictions, participants with aMCI were substantially impaired on an easy focal event-based PM task when compared to healthy controls, but the difference between the groups on a more demanding nonfocal PM task was not statistically significant. In other words, while healthy older adults showed a standard cue-focality effect with significantly reduced performance on a nonfocal than focal task, the aMCI group's performance on the focal PM task was not statistically different from that of the nonfocal task. It is important that this interaction was obtained with a well-defined group of single domain aMCI participants, using an engaging ongoing task of recognizing professions of famous people, without any ceiling or floor effects on any of the dependent variables. In addition, the fact that we individually calibrated the processing time of the ongoing task probably explains the absence of group effect in a more difficult nonfocal PM task, which is relatively rare in the literature (but see Chi et al., 2014; McDaniel et al., 2011). Indeed, in most studies using either experimental PM tasks or a particular PM test battery, the overall task demands were markedly higher for participants with aMCI or very mild AD.

Second, results concerning self-reported rehearsal and a novel measure of overt rehearsal fully supported the predictions of multiprocess theory. In both groups, strategic monitoring was significantly higher in the nonfocal than focal PM conditions, and

[5] Because the variables of self-rated and overt rehearsals were not normally distributed, we also ran series of nonparametric tests and correlations, but they produced identical findings.

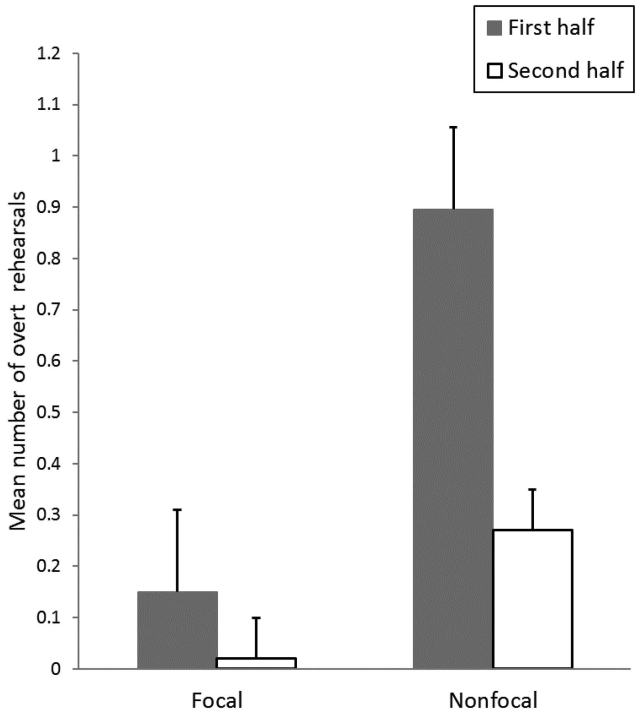

Figure 3. Mean number of overt rehearsals (with standard errors of the mean) as a function of ongoing task half (first vs. second) and prospective memory cue (focal vs. nonfocal).

monitoring rates correlated with PM scores in the nonfocal, but not in the focal PM task. Importantly, there were no group differences in the amount of self-reported and overt rehearsals (i.e., strategic monitoring). Together, these findings confirm that it was the spontaneous retrieval processes in the focal PM task that were particularly disrupted in the aMCI participants. Moreover, the finding that self-reported and overt (behavioral) measures of rehearsal were positively correlated in both groups indicates that aMCI participants did not over- or underestimate their monitoring due to problems with retrospective memory.

Taken together, these findings have significant implications for current theoretical understanding of cognitive processes most disrupted in the transitional stages between normal aging and the AD, and for early detection of cognitive decline. Below, we discuss possible advantages of using focal PM as an early cognitive marker of the AD and brain mechanisms underlying focal PM deficits in aMCI. Finally, based on the structural and functional neuroimaging data on the brain's default network and initial results from behavioral studies, we propose a novel hypothesis of more generic spontaneous retrieval deficits in aMCI.

Focal PM as an Early Cognitive Marker of the AD

Despite intensive research on early cognitive markers of AD, there is no universal agreement about which particular memory tasks have the best diagnostic accuracy in discriminating healthy older adults from aMCI. The dominant view is that long-term (retrospective) episodic memory tasks are the best available tests for detecting cognitive decline in aMCI and AD (Gainotti et al., 2014), with some studies emphasizing the importance of measuring paired associate learning and others delayed free recall of words or stories (Didic et al., 2011; Dubois et al., 2007). Deficits in performing these tasks is thought to map onto the first signs of brain pathology in the hippocampus at the early stages of the disease. However, the medial temporal lobe and the hippocampus serve multiple functions and are not only involved in long-term episodic memory, but also in short-term relational binding including perceptual matching tasks that do not contain any delays (e.g., Hannula & Ranganath, 2008; Lee, Scahill, & Graham, 2008).

Most importantly, almost all currently used memory tests (whether long- or short-term) require deployment of deliberate and effortful strategies at encoding and retrieval, which rely on prefrontal structures in both normal and cognitively impaired adults (e.g., Lekeu et al., 2003). Given that prefrontal areas get compromised at later stages than medial temporal lobes (Braak & Braak, 1991), it is highly likely that partial compensation takes place in people with aMCI and mild AD, reducing the sensitivity of standard tests to detect subtle changes in the medial temporal lobes and/or the posterior parts of the default network that have dense connections with each other. Therefore, episodic memory tasks that depend less on the prefrontal cortex should have better discriminatory power than the currently used tests.

Moreover, Logie, Parra, and Della Sala (2015) have proposed a set of criteria that a good cognitive marker should satisfy. The most important of these are that the task is age invariant and disease specific, so that other disorders can be eliminated. None of the currently used standard delayed episodic memory tests are age invariant (i.e., they all show impairments in healthy older adults), nor are they disease specific, as performance on these tests is also impaired in other conditions (e.g., in depression). In contrast, focal event-based PM tasks satisfy the key requirement of age invariance, as age effects are absent or small in healthy adult population (see Kliegel et al., 2008). Moreover, the decrement in focal PM in patients with aMCI appears to be disease specific, as participants with clinical depression or Parkinson's disease have demonstrated the same pattern as normally aging adults, that is, preserved performance on focal event-based tasks and significantly impaired performance on nonfocal event-based tasks (Altgassen, Kliegel, & Martin, 2009; Foster, McDaniel, Repovs, & Hershey, 2009). Thus, focal event-based PM tasks may be one of the few long-term episodic memory tasks that are age invariant and specific to AD, and could be potentially considered as the best early cognitive markers of the disease (cf. Huppert & Beardsall, 1993; McDaniel et al., 2011).

Brain Mechanisms Underlying Focal PM Deficits in aMCI

This raises an important question about brain mechanisms that support spontaneous retrieval processes in focal PM tasks and how they map onto pathological changes observed at preclinical and MCI stages of the disease. Despite a large body of research on brain mechanisms involved in PM (Cona, Scarpazza, Sartori, Moscovitch, & Bisiacchi, 2015), there is very little research on brain mechanisms involved in focal PM tasks, or how they may differ from those involved in nonfocal PM tasks. According to the dual pathways neurocognitive model of PM, that is based on the multiprocess theory of PM, focal PM tasks are less dependent on

prefrontal structures, especially on the anterior prefrontal cortex (BA10), which has been implicated in more attentionally and strategically demanding PM tasks (McDaniel, Umanath, Einstein, & Waldum, 2015; see also McDaniel & Einstein, 2007, 2011). Instead, at retrieval, in the presence of a focally processed cue, the representation of intention should be automatically delivered by hippocampus and nearby structures in the medial temporal lobe, which are assumed to support spontaneous and obligatory associative retrieval processes in response to strong cues (Konkel & Cohen, 2009; Moscovitch, 1994).

The most direct evidence in support of this idea comes from a study by Gordon, Shelton, Bugg, McDaniel, and Head (2011), who showed a positive correlation between scores on a focal (but not for a nonfocal) PM task and gray matter volume in medial temporal lobe structures (especially in hippocampus) in a sample of older adults with and without mild AD. Indirect evidence comes from two studies on normally functioning children and adolescents born preterm (Ford et al., 2016 and Isaacs et al., 2003, respectively), who are known to have mild hippocampal atrophy. For example, a sample of adolescents in Isaacs et al. (2003), had an average bilateral hippocampal atrophy of only 8%–9%. In both studies, significant differences between participants born preterm and age matched controls were obtained in PM tasks that relied predominantly on spontaneous retrieval processes, while no group differences emerged on numerous tests of episodic (retrospective) memory. Taken together, results of these studies support the idea that in comparison to standard episodic memory tests, focal PM tasks may be sensitive to even small hippocampal atrophy that may be present in the aMCI or preclinical stages of the disease.

In contrast, evidence from brain imaging studies is more varied and difficult to interpret, showing distinct as well as overlapping structures that are activated in focal and nonfocal tasks (e.g., Cona et al., 2015; McDaniel et al., 2015). In addition, by and large, they have failed to demonstrate transient hippocampal activations in focal PM tasks. This could be due to weak activations that cannot be picked up reliably without very high resolution technology (cf. Cona et al., 2015; McDaniel et al., 2015).

However, a recent meta-analysis of imaging studies that investigated either focal or nonfocal PM, or both, showed that the most important differences between focal and nonfocal tasks emerged in the retrieval phase (Cona, Bisiacchi, Sartori, & Scarpazza, 2016). For example, higher activations in nonfocal than focal tasks were found in the left lateral anterior prefrontal cortex (BA 10) and in the anterior cingulate cortex. In contrast, higher activations in focal than nonfocal PM tasks were found in the posterior cingulate cortex (BA 31), ventral parietal regions, such as the inferior parietal lobule and the supramarginal gyrus (BA 40), and the cerebellum. These dissociations, according to the authors, indicate that the retrieval of nonfocal PM tasks is primarily mediated by top-down and stimulus independent strategic processes, while focal tasks are mediated by more bottom-up automatic retrieval processes.

Beck, Ruge, Walser, and Goschke (2014) also showed transient PM cue-related activations in the bilateral ventral parietal cortex, the precuneus and the posterior cingulate cortex in response to PM cues that occurred in a post-PM block where participants did not have to perform the PM task (and hence did not monitor for cues). Therefore, the available evidence from imaging studies seems to converge on the involvement of the posterior cingulate cortex and the ventral parietal cortex (including the inferior parietal lobule) in the spontaneous bottom-up retrieval processes in focal PM tasks.

The involvement of these posterior brain areas in focal PM tasks is important because they constitute key parts of the brain's default network, especially the posterior cingulate cortex and the inferior parietal lobe, which not only have anatomical connections with the medial temporal lobe structures, but also functional correlations in resting state fMRI studies (Buckner et al., 2005; Leech & Sharp, 2014; Vincent et al., 2006). Given that amyloid depositions are particularly likely to affect these default network areas in preclinical stages of the disease, and even in healthy older adults (Elman et al., 2016; Sperling et al., 2009), it is possible that the focal PM performance is particularly sensitive to these abnormal changes in the brain at very early and prodromal stages of AD. Moreover, Pengas, Hodges, Watson, and Nestor (2010), using volumetric MRI, showed that aMCI patients, who all subsequently converted to AD, had a significant atrophy in posterior cingulate cortex (BA23 and BA 29/30), comparable with their hippocampal atrophy (see also Nickl-Jockschat et al., 2012).

Therefore, it is possible that aMCI participants in our study showed significant disruptions in the focal PM task because of the functional and structural changes in the default network (especially in its posterior parts). There is also evidence that focal PM depends on medial prefrontal cortex regions (e.g., BA 9; Cona et al., 2016; McDaniel et al., 2015), that constitute another important hub of the default network with direct anatomical and functional connections with the posterior cingulate cortex as well as medial temporal lobe structures (Buckner, Andrews-Hanna, & Schacter, 2008).

The Spontaneous Retrieval Deficit Hypothesis

Based on these considerations, and growing evidence of the involvement of the default network in spontaneous cognitive phenomena such as mind-wandering and involuntary autobiographical memories (Andrews-Hanna, Reidler, Huang, & Buckner, 2010; Andrews-Hanna, Smallwood, & Spreng, 2014; Buckner et al., 2008), we propose that the disproportionate disruption of focal PM in aMCI and very mild AD could be only one particular manifestation of a more global deficit in spontaneous retrieval processes involved in a variety of (declarative) cognitive phenomena, which rely heavily on the coordinated operation of different parts of the default network, including the dorsal and ventral medial prefrontal cortex, posterior cingular cortex/retrosplenial cortex, inferior parietal lobule, medial temporal lobe and the hippocampus (Buckner et al., 2008).

Initial support for this idea comes from a study by Jackson, Fagan, Holtzman, Balota, and Morris (2012) on mind-wandering using a standard sustained attention to response task with additional thought probes in which participants indicated if they were on task or off task. The results showed that participants with the mild AD reported fewer (spontaneous) task unrelated thoughts than healthy controls. Similarly, Niedzwienska and Kvavilashvili (in preparation) engaged participants in an easy vigilance task, with irrelevant cue words on some trials and occasional thought probes in which participants reported what was going through their mind (modified from Plimpton, Patel, & Kvavilashvili, 2015). In line with the spontaneous retrieval deficit hypothesis, it was found that aMCI participants had significantly fewer spontaneous task unrelated thoughts than healthy controls, even though the vigilance

task performance was at ceiling in both groups. In addition, aMCI participants reported significantly fewer memories from the past or involuntary autobiographical memories (Berntsen, 2010; Schlagman & Kvavilashvili, 2008). The aMCI participants' inability to spontaneously experience past memories in response to irrelevant cue words is particularly interesting and indicates a general disruption in conscious spontaneous reflexive/associative processes in response to cues, irrespective whether one is dealing with focal PM tasks, involuntary memories, or mind-wandering.

Avenues for Future Research

Taken together, the results of the present study and the spontaneous retrieval deficit hypothesis open up several important avenues for future research. First, it is necessary to launch a systematic, more targeted investigation of brain mechanisms of focal PM tasks and the relationship between focal PM scores and structural/functional changes in the medial temporal lobe, hippocampus and posterior (as well as other) parts of the default network. Second, it is important to examine if focal PM tasks can discriminate healthy older adults from individuals with subjective cognitive impairment (SCI), who have subjective memory complains, but perform within age-appropriate norms on standard tests of episodic memory (Jessen et al., 2014). Given that adults with SCI have enhanced rates of conversion to AD and show brain pathology characteristic of the disease (Sperling et al., 2011; Stewart et al., 2011; Wang et al., 2013), it is important to develop and test cognitive tasks that are sensitive to SCI individuals' self-perceived deficits in everyday life (e.g., see Rentz et al., 2013). There are only a few studies on PM in SCI with contradictory results (Chi et al., 2014; Hsu, Huang, Tu, & Hua, 2015; Rabin et al., 2014), and none of them have compared clearly defined focal and nonfocal PM tasks (but see Chi et al., 2014). Third, there is a clear need for prospective longitudinal studies to examine the ability of focal PM tests to predict the conversion rates of aMCI to AD, in addition to testing the diagnostic accuracy of focal PM tasks in cross sectional studies. Finally, the spontaneous retrieval deficit hypothesis needs to be tested in such cognitive domains as involuntary autobiographical memories, spontaneous future thinking, and involuntary musical imagery, to name the few (Berntsen & Jacobsen, 2008; Floridou & Müllensiefen, 2015; Plimpton et al., 2015; Williams, 2015). If the findings reported in this study are extended to these various spontaneous cognitive phenomena not only in individuals with aMCI, but also in those with SCI, then this can radically change our theoretical understanding of cognitive processes most disrupted in preclinical stages of AD, and significantly improve the process of clinical diagnosis in MCI and AD.

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Received September 23, 2016
Revision received March 18, 2017
Accepted March 21, 2017 ■