through development, we then need to examine whether adults with early-onset damage to the anterior medical PFC show any deficit in theory of mind performance.

Previous studies have reported functional abnormality in the medial PFC in autism-spectrum disorders during social task performance like theory of mind reasoning (Di Martino et al., 2009 Based on the model by Hoekstra et al. (2008), autism personality traits detected in AQ were divided into "social interaction" and "attention to detail" factors. Considering our result that nearly all items for the development of autistic personality traits in both cases fell into the "social interaction" factor, the medial prefrontal area does not seem to be involved in the personality trait for "attention to detail". Functional abnormality in the medial PFC in autism-spectrum disorders is likely to be associated with a lack of social interaction.

The present study remains preliminary, but some essential implications help in understanding the possible roles of the medial PFC. More research is evidently required to confirm the hypotheses discussed in this study. Besides theory of mind functioning, several recent neuroimaging studies have shown that the medial PFC is involved in moral judgment (Greene, Sommerville, Nystrom, Darley, & Cohen, 2001), self-referential processing (Kelley et al., 2002; Schaefer, Berens, Heinze, & Rotte, 2006), memory for self (Macrae, Moran, Heatherton, Banfield, & Kelley, 2004), and detecting the communicative intentions of others (Kampe, Frith, & Frith, 2003). If we expand our discussion by extending the region of interest from the medial PFC to the adjacent anterior cingulate cortex, arguments can be made from the perspectives of cognitive control (MacDonald, Cohen, Stenger, & Carter, 2000), error detection or online monitoring (Carter et al., 2000). Furthermore, the influence of damage to other "social brain" areas needs to be examined. As a recent meta-analysis indicated, the right anterior insula was found to be hypoactive in autism-spectrum disorders compared to the neurotypical control (Di Martino et al., 2009). This area is known to be involved in empathy processing (Singer et al., 2004, 2006). As well as the superior temporal sulcus, amygdala, and posterior cingulate, further examination of the influence of selective damage to these areas on theory of mind performance is required.

Finally, from a comparative neurocognitive perspective, the medial PFC is sure to be an essential area in reaching a full understanding of the development or evolution of social communications (Rushworth, Walton, Kennerley, & Bannerman, 2004). A morphological study indicated large spindle-shaped cells in layer Vb of the anterior cingulate cortex in pongids and hominids, but not in any other primate species or mammalian taxa (Nimchinsky et al., 1999). Although the ways in which spindle cells contribute to social functions of the anterior cingulate cortex remain unclear, this observation is obviously of great interest in attempts to clarify the mechanisms of possible evolutional changes to adapt to social worlds.

In sum, we have reported two neurological cases with damage to the medial PFC, focusing on theory of mind performance and personality change. Following damage to this area, both cases showed no impairment on standard theory of mind tests and mild impairments on advanced theory of mind tests. Interestingly, personality changes were found in both cases after surgical operations, leading to characteristics of autism mainly presenting as a lack of social interaction. Recent studies have shown that the medial PFC is involved in various kinds of theory of mind tests. The medial PFC is presumably required for efficient realization in theory of mind reasoning, but such reasoning may receive support from other brain areas in adults. If the medial PFC plays an important role in theory of mind reasoning through development, the critical question in understanding its functions would be whether adults with early-onset damage to the medical PFC show any deficit in theory of mind performance.

Manuscript received 13 December 2007
Manuscript accepted 21 April 2009
First published online 27 July 2009

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G Model
NSY-4090; No. of Pages 7
ARTICLE IN PRESS

Neuropsychologia xxx (2011) xxx–xxx

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Deficits in prospective memory following damage to the prefrontal cortex

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ARTICLE INFO

Article history:
Received 26 August 2010
Received in revised form 25 March 2011
Accepted 28 March 2011
Available online xxx

Keywords:
Prospective memory
Prefrontal cortex
Medial temporal lobe
Neuropsychological test
Executive function
Traumatic brain injury

ABSTRACT

Neuropsychological investigations of prospective memory (PM), representing memory of future intentions or plans, have evolved over the past two decades. The broadly accepted divisions involved in PM consist of a prospective memory component (PMC), a process for remembering to remember, and a retrospective memory component, a process for remembering the content of the intended action. Previous functional neuroimaing studies have provided some evidence that the rostral prefrontal cortex (BA10) is one of areas that is critical for prospective remembering. However, the question of whether damage to part of the prefrontal cortex affects attenuated performance for PMC remains unresolved. In this study, 74 participants with traumatic brain injury (TBI) including focal damage to frontal or temporal lobe areas were administered thirteen standard neuropsychological tests and the PM task. To identify influential areas contributing to PM performance, discriminant function analysis was conducted. The results indicated that the following three areas are highly contributory to PM performance: the right dorsolateral prefrontal cortex; the right ventromedial prefrontal cortex; and the left dorsomedial prefrontal cortex. Comparing differences in neuropsychological test scores showed that orientation scores were significantly higher in the greater PM performance group, suggesting that PMC represents an integrated memory function associated with awareness of current status. These data contribute to our understanding of the neural substrates and functional characteristics of the PMC.

1. Introduction

Neuropsychological investigations of prospective memory (PM), representing memory involving future intentions or plans, have evolved over the past two decades. This area of research can be divided into two types. The first involves studies into neurological examinations of various types of disorders, including Alzheimer's disease (AD) or mild cognitive impairment (MCI) (Blanco-Campal, Coen, Lawlor, Walsh, & Burke, 2009; Costa et al., 2010; Thompson, Henry, Rendell, Withall, & Brodaty, 2010; Troyer & Murphy, 2007), Parkinson's disease (Costa, Peppe, Caltagirone, & Carlesimo, 2008; Foster, McDaniel, Repovs, & Hershey, 2009), multiple sclerosis (MS) (West, Mcnerney, & Krauss, 2007), schizophrenia (Henry, Rendell, Kliegel, & Altgassen, 2007; Kumar, Nizamie, & Jahan, 2005; Woods, Twamley, Dawson, Narvaez, & Jeste, 2007), substance abuse (Paraskevaides et al., 2010), developmental disorders (Brandimonte, Filippello, Coluccia, Altgassen, & Kliegel, 2011; Jones et al., 2010), and HIV infection (Gupta, Woods, Weber, Dawson, & Grant, 2010; Woods et al., 2008). Although most of these studies intended to investigate the neural substrates of prospective memory, some studies aimed to determine whether PM performance could be a diagnostic criterion for AD, MCI and other types of dementia (Blanco-Campal, Coen, Lawlor, Walsh, & Burke, 2009; Huppert & Beardsall, 1993; Maylor, 1995). The weight of evidence seems to support the positive position that PM performance could be a diagnostic criterion (Jones, Livner, & Bäckman, 2006), although some evidence supports the negative position (Livner, Laukka, Karlsson, & Bäckman, 2009).

The second type of research involves participants with focal damage to certain areas in the brain. Several studies have shown that the frontal and medial temporal lobes are necessary for successful prospective remembering (Cockburn, 1995; Umeda, Nagumo, & Kato, 2006). To investigate PM performance in participants with brain damage, two different types of experimental paradigm, event-based PM and time-based PM, have often been used, along with behavioral experiments (Einstein & McDaniel, 1990). Participants are generally instructed to busily engage in a background task during which words are presented on a computer screen, and they are asked to recall them after all of the words have been presented. Participants in the event-based PM task are then instructed to press a pre-determined key on a keyboard whenever a target word that was learned prior to the task appears, while participants in time-based PM tasks are instructed to press a pre-determined key after a certain time has elapsed. These exper-

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0028-3932/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropsychologia.2011.03.036

Please cite this article in press as: Umeda, S., et al. Deficits in prospective memory following damage to the prefrontal cortex. *Neuropsychologia* (2011), doi:10.1016/j.neuropsychologia.2011.03.036

imental frameworks generate highly controlled data that allow discussion of the mechanisms underlying prospective remembering. An early neuropsychological study using event-based and time-based PM tasks found that one patient with a frontal lobe lesion had no difficulties in event-based tasks, but showed a decline in some time-based tasks (Cockburn, 1995). That patient thus failed to recall intended actions spontaneously within an appropriate time after the frontal lobe was damaged. The same deficits have been found by other tests in patients with frontal lobe damage (Shallice & Burgess, 1991). These deficits have been explained from various perspectives, such as loss of ability to plan, spontaneous processing, and use of a retrieval strategy (Burgess & Shallice, 1997; Worthington, 1999).

Other brain areas besides the frontal lobe are also involved in prospective remembering. Previous studies have demonstrated various types of memory disorder following lesions in the medial temporal lobe, including the hippocampus, parahippocampus, and surrounding areas (Umeda et al., 2006). Few studies, however, have reported data suggesting selective deficits of prospective memory in patients with a medial temporal lobe lesion, as most cases with damage to this area show light or severe anterograde amnesia. Moreover, a related study found that adults who had been born preterm exhibited a mean bilateral reduction in hippocampal volume of 8–9% and significant impairment relative to controls on only a few memory measures, including prospective memory measures (Isaacs et al., 2003).

Behavioral studies have revealed many distinctive characteristics of PM (Brandimonte, Einstein, & McDaniel, 1996). The most prominent appears to be the component division involved in PM (Einstein & McDaniel, 1990). The first component is a process for *remembering to remember* or *prospective memory component (PMC)*: the individual who intends to do something in the future must first remember that this action needs to be taken. Spontaneous retrieval with appropriate timing is necessary for successful remembering to remember, since there are no obvious cues for directly remembering intended actions in usual everyday situations. Prospective memory is also described as "more than just memory," as sensitivity to the passage of longer periods of time and timing-based spontaneous retrieval is crucial to allow intentions to come to mind. The second component is a process for *remembering content* or *retrospective memory component (RMC)*: even when the individual remembers to remember, they still have to remember what needs to be done in order to fulfill the intention properly, and some external memory cues or devices are useful for remembering content. An intention can be realized only when these two components are appropriately processed.

A number of neuropsychological findings also support this division. An early study examined prospective remembering in older adults by assessing frontal lobe function and medial temporal lobe function using an event-based prospective memory task. The results showed that high-functioning frontal participants showed better prospective remembering than low-functioning frontal participants and no significant difference was found in prospective memory performance for medial temporal functioning (McDaniel, Glisky, Rubin, Guynn, & Routhieaux, 1999). A number of previous psychophysiological studies using event-related brain potentials (ERPs) have indicated that the realization of delayed intentions is associated with distinct components of ERPs that are related with the detection of a PM cue in the environment (N300), the retrieval of an intention from memory, signaling the need to switch from the ongoing activity (frontal positivity), and configuration of the PM task set (parietal positivity) (West, 2011; West & Bowry, 2005; West, Bowry, & Krompinger, 2006; West, McNerney, & Travers, 2007). These data support the PMC–RMC distinction and the notion that some components involved in PMC depend on frontal lobe functions.

As a neuropsychological study of patients, Henry, Phillips, et al. (2007) reported that traumatic brain injury (TBI) patients were significantly and comparably impaired on one- and four-target-event conditions relative to controls, suggesting that TBI deficits in PM could not be attributed to increased difficulty in the RMC of the PM task. In another study, independent neural contributions of these two components were examined using the PM training procedure, and the findings suggested that the prefrontal cortex is required for PMC, whereas the medial temporal lobe is required for RMC (Umeda et al., 2006). Previous neuroimaging studies have also supported this notion and that the prefrontal cortex is essentially involved in the PMC (see Section 4). Furthermore, Kliegel, Eschen, and Thöne-ottoc (2004) proposed that the realization of delayed intentions is composed of four phases: intention formation, retention, re-instantiation, and execution. They demonstrated that TBI patients with retrospective memory within normal limits, but impaired executive functions, showed attenuated performance in the intention formation, re-instantiation and execution phases and intact performance in the retention phase. This suggests the PMC is not exclusive, but is composed of multiple processes and mostly independent from the RMC.

As a neuroimaging approach to prospective memory, an early positron emission tomography (PET) study showed that some brain regions, including the right dorsolateral and ventrolateral prefrontal cortex, the left frontal pole, and the left parahippocampal gyrus in the medial temporal lobe, were activated when subjects were engaged in a prospective memory task (Okuda et al., 1998). The involvement of the prefrontal cortex including the rostral PFC (BA10) was also observed in other PET studies (Burgess, Quayle, & Frith, 2001; Burgess, Scott, & Frith, 2003) Another functional magnetic resonance imaging (fMRI) study indicated that PM success was predicted by activations in the left rostrolateral PFC and right parahippocampal gyrus (Poppenk, Moscovitch, McIntosh, Ozcelik, & Craik, 2010) (see also Section 4 for details).

These findings provide evidence supporting the independent neural contributions of the PMC–RMC division and the involvement of multiple areas within bilateral prefrontal and medial temporal areas in prospective remembering. From a more detailed perspective, however, the question of whether damage to part of the prefrontal and medial temporal areas affects attenuated performance for PMC remains unresolved. The main goal of the present study was to identify a more precise neural basis for PMC. To obtain reliable results for this type of neuropsychological study, a large number of patients with focal brain damages must be recruited. The present study included a total of 74 patients with TBI showing focal damages to the frontal or temporal lobe area. Based on findings for the damaged area in each participant, we used discriminant function analysis to identify the responsible neural bases for PMC.

2. Methods

2.1. Participants

We first recruited a total of 81 patients with TBI showing focal damage to the frontal or temporal lobe area. Patients selection was based on a consecutive series of clinical investigations and nearly half of the patients were tested as in-patients. The inclusion criteria were as follows: (1) high onset arousal level (mean Glasgow Coma Scale (GCS) score was 13.0), (2) the presence of focal damage in the frontal or temporal lobe area, not only the presence of diffuse axonal injury (DAI), (3) no other neurological or psychiatric history, (4) no history of drug abuse, and (5) no previous participation in rehabilitation.

All participants were administered the PM task (see Section 2.2.3 for details) and only 7 participants showed difficulty in recalling the contents of the action required at the beginning of the experimental session, even after being given multiple retrieval cues. We then removed those 7 participants to concentrate on the neural substrates of PMC.

Mean age of the 74 participants was 39.5 years (range, 15–67 years), and mean duration of education was 11.8 years. All patients had traumatic brain injuries in focal regions involving the frontal or temporal lobe area. The participants were in stable or chronic status from the onset of injury (mean duration from onset of injury

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to testing, 35.0 days). No significant correlation was identified between score for the PM task (see Section 2.2.3) and the duration from onset of the injury ($r = -.006$, $p > .10$). All participants gave their informed consent prior to participation in this study.

2.2. Procedure

2.2.1. Radiological investigation

All participants underwent computed tomography (CT) and MRI to identify damaged areas of the brain. Based on previous neuropsychological and neuroimaging studies of prospective memory, for the present study, we selected a total of twelve brain regions as central areas for examining the effects of damage (e.g., Burgess & Shallice, 1997; Burgess, Dumontheil, & Gilbert, 2007; Reynolds, West, & Braver, 2009; Shallice & Burgess, 1991; Simons, Scholvinck, Gilbert, Frith, & Burgess, 2006; Umeda et al., 2006). In terms of the frontal lobe, we examined whether the damage was found in each of the following areas: (1) right and (2) left dorsolateral prefrontal cortex (DLPFC) including Brodmann area (BA)9 and the superior parts of BA10 and BA46; (3) right and (4) left ventrolateral prefrontal cortex (VLPFC) including BA11, BA47 and the inferior parts of BA10 and BA46; (5) right and (6) left dorsomedial prefrontal cortex (DMPFC) including BA9 and the superior parts of BA10; and (7) right and (8) left ventromedial prefrontal cortex (VMPFC) including BA11 and the inferior parts of BA10. In terms of the temporal lobe, we examined whether damage was evident in each of the following areas: (9) right and (10) left lateral temporal cortex, outside the inferior horn of the lateral ventricle; and (11) right and (12) left medial temporal cortex, inside the inferior horn of the lateral ventricle. These twelve factors were used as independent variables in the following discriminant function analysis.

The identification of lesion location was based on independent careful visual inspections by at least two specialists, including a radiologist and a neurosurgeon. The mean number of damaged areas (among the 12 areas listed above) in each participant was 2.2 ($SD = 1.2$), with a maximum of 6. Sixty of the 74 participants showed damage in less than 3 areas, meaning that areas of brain damage were relatively focal.

2.2.2. Neuropsychological assessment

All participants were administered standard neuropsychological tests to assess intelligence quotient (IQ), general memory, attention and other higher cognitive functions. These tests included: (1) Raven's Coloured Progressive Matrices (RCPM: Raven, Court, & Raven, 1990) Set B; (2) Kohs Block Design Test (Kohs, 1923); (3) Hasegawa Dementia Scale – Revised (HDS-R: Imai & Hasegawa, 1994): (a) Total score, (b) Orientation, and (c) Repeating 3 words; (4) Digit span (in WMS-R: Wechsler, 1987): (a) Forward, and (b) Backward; (5) Visual memory span (in WMS-R): (a) Forward, and (b) Backward; (6) 7 Words memory test (Handa, 1989); (7) Wisconsin Card Sorting Test (WCST: Heaton, 1981): (a) Categories Achieved (CA), (b) Perseveration Errors (PE), and (c) Difficulty of Maintaining Set (DMS); (8) Verbal fluency: (a) Category ("vegetable"), and (b) Initial letter ("ta") (Imai & Hasegawa, 1994); and (9) Serial Seven Subtraction Test (in MMSE, Folstein, Folstein, & McHugh, 1975). All tests including the subsequent PM task were administered by the same experimenter.

2.2.3. Evaluation of prospective memory performance

To assess PM performance in participants, a simple PM task similar to the subtest for "belonging" in the Rivermead Behavioral Memory Test (RBMT) was embedded in the neuropsychological assessment tests (Wilson, Cockburn, & Baddeley, 1985). At the beginning of the standard neuropsychological test session, participants were handed a number-card ("18" on it) and asked to return the card at the end of the experiment. At that point, we confirmed that they placed the card into their pocket or bag, out of the participant's fields of view.

At the end of the tests, which lasted approximately one hour, we stated the tests had ended and checked whether the participant spontaneously correctly remembered the PM task to return the number-card. If the required action was not performed, Prompt A was given, as "Didn't you forget to do something?". If no response was made within 10 s, Prompt B was given, as "I handed you something to return." As stated above, 74 of 81 participants were able to perform the required action (returning the number-card) either without or with prompting.

A result of "success" was recorded when the patient performed the action within the appropriate time with no prompt and "failure" when they performed the correct action with Prompt A or B. Thus, spontaneous prospective memory retrieval with no prompt reflects the PMC component, whereas cued retrieval with Prompt A only or Prompts A and B reflects the RMC component. The test–retest reliability of this task has already been examined (Umeda, Kato, Mimura, Kashima, & Koyazu, 2000). The rate of agreement between the score on the first test and that of the second test, which was administered three months after the first test, was .86, which is considered to be high.

Table 1
Scores for standard neuropsychological tests.

	Success in PMT ($n = 32$)	Failure in PMT ($n = 42$)
Mean age (years)	38.3 (16.1)	40.2 (15.7)
Mean education (years)	11.3 (2.3)	12.2 (2.6)
RCPM: Set B/12	7.5 (2.9)	8.0 (3.1)
Kohs Block Design Test (IQ)	76.8 (26.8)	78.3 (27.7)
Hasegawa Dementia Scale – Revised (HDS-R)		
Total score/30	24.0 (4.9)	21.5 (4.9)*
Orientation/7	6.6 (0.7)	5.8 (1.4)**
Repeating 3 words/6	4.1 (2.2)	3.4 (2.0)
Digit span		
Forward	5.2 (1.0)	5.5 (1.2)
Backward	3.8 (1.3)	3.9 (1.2)
Visual memory span		
Forward	5.4 (1.0)	5.5 (1.1)
Backward	4.7 (1.4)	4.7(1.1)
7 Words memory test/7	6.1(1.2)	6.0 (1.0)
Wisconsin Card Sorting Test (WCST)		
Categories achieved (CA)/6	2.8 (2.1)	2.8 (2.2)
Perseveration errors (PE)	12.6 (13.0)	11.8 (11.6)
Difficulty of maintaining set (DMS)	0.9 (1.1)	1.1 (1.4)
Verbal fluency		
Category ("vegetable")	8.9 (4.4)	7.9 (3.8)
Initial letter ("ta")	3.8 (2.8)	4.0 (2.6)
Serial Seven Subtraction Test/4	2.6 (1.4)	2.0 (1.6)

Note. PMT, prospective memory task; RCPM, Raven's Coloured Progressive Matrices; numbers in parentheses represent standard deviations (SDs).
* $p < .05$.
** $p < .01$.

3. Results

3.1. Prospective memory performance and neuropsychological test profile

Among all 74 participants, 32 participants were sorted into the "success" group, performing the required action within the appropriate time. The remaining 42 were sorted into the "failure" group, unable to perform the action spontaneously, but able to perform it with Prompt A or B.

To compare differences in neuropsychological test scores between groups, we calculated average scores for the tests (Table 1). Statistical testing revealed significant differences between two groups only for total and orientation scores of the HDS-R, with higher scores in the "success" group (total score: $t(72) = 2.21$, $p < .05$; orientation score: $t(72) = 2.95$, $p < .01$). Careful observation of the data seemed to show no specific pattern of ceiling or floor effects. Although age was not found to be a significant variable that explains the differences in performance in the prospective memory task, we investigated whether participant age is a predicator of performance on the prospective memory task in all participants. However, no significant correlation was observed between age and performance ($r = -0.162$, $p > .10$).

3.2. Discriminant function analysis for prospective memory performance

To identify variables contributing to performance in the PM task, discriminant function analysis was conducted, using damage to each participant in the twelve specific areas (as described in Section 2.2.1) as independent variables, and group "success" or "failure" in the PM task as the grouping variable. Stepwise discriminant function analysis indicated three variables that minimized Wilk's lambda value. Analysis identified the following areas as highly contributing functions: "right dorsolateral prefrontal cortex" in Step 1 (Wilks' s lambda = .930, $F(1, 72) = 5.45$, $p < .05$), "right ventromedial prefrontal cortex" in Step 2 (Wilks' s lambda = .894, $F(1, 71) = 4.22$,

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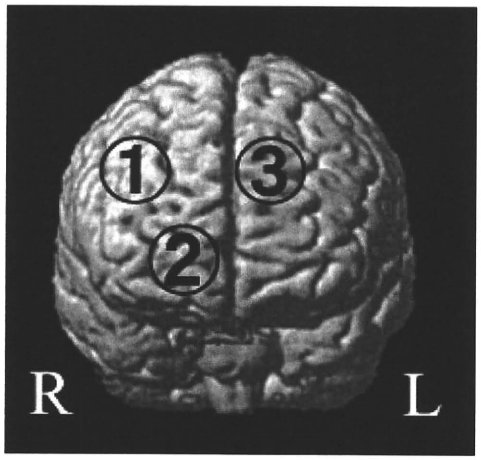

Fig. 1. Areas identified as contributing significantly to performance in the prospective memory task: (1) right dorsolateral prefrontal cortex, (2) right ventromedial prefrontal cortex, and (3) left dorsomedial prefrontal cortex.

$p < .05$), and "left dorsomedial prefrontal cortex" in Step 3 (Wilks's lambda = .865, $F(1, 70) = 3.65$, $p < .05$) (Fig. 1). Overall, these three variables accounted for 67.6% of the correct classification matrix.

In order to evaluate the specificity of the results obtained, multiple linear regression analysis using Hayashi's quantification method type-I (Hayashi, 1952) was conducted separately for the following sixteen neuropsychological tests measures, using damage to each participant in the twelve specific areas as independent variables, and score of each neuropsychological test as the dependent variable: (1) RCPM, (2) Kohs, (3) HDS-R Total score, (4) HDS-R Orientation, (5) HDS-R Repeating 3 words, (6) Digit span Forward, (7) Digit span Backward, (8) Visual memory span Forward, (9) Visual memory span Backward, (10) 7 Words memory test, (11) WCST Categories Achieved, (12) WCST Perseveration Errors, (13) WCST Difficulty of Maintaining Set, (14) Verbal fluency Category, (15) Verbal fluency Initial letter, and (16) Serial Seven Subtraction Test. Analysis identified the following areas as having a significant contribution: "left medial temporal cortex" on test (3), (5), (7), and (14); "right dorsolateral prefrontal cortex" on test (2), (11), and (16); "right dorsomedial prefrontal cortex" on test (3), and (5); "left ventrolateral prefrontal cortex" on test (5); and "right ventrolateral prefrontal cortex" on test (11) (all $p < .05$). The pattern of these results was not similar to the finding of the discrimanant function analysis. It is important to note that a set of three areas (right dorsolateral prefrontal cortex, right ventromedial prefrontal cortex, and left dorsomedial prefrontal cortex) were identified by the discriminant function analysis as being significantly involved in PM performance.

4. Discussion

The main goal of the present study was to identify the neural bases responsible for PMC using discriminant function analysis. This analysis revealed three areas as highly contributing factors to PM performance. The pattern of these results obtained for PM performance, was not similar to the finding from the multiple linear regression analysis for other neuropsychological tests. This difference suggests that these three areas are specifically involved in PMC. Therefore, based on previous neuroimaging and neuropsychological findings, we consider that cognitive functions are located in each area.

Results indicated that the right DLPFC was the primary factor influencing PM task performance. Past neuroimaging studies have shown that the right DLPFC is highly correlated with working memory performance (Braver et al., 1997). In a subsequent study, the right DLPFC was proposed to have a function in working memory selection from memory to guide a response (Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000). Similarly, the area was considered to be involved in task switching based on the fact that task switching yielded activation of this area (Sohn, Ursu, Anderson, Stenger, & Carter, 2000). Neural substrates for supporting PMC are considered to share in the maintenance of information for intended actions, selection of the required action among candidate actions, and sensitivity to the context or cue that may have changed over time.

Discriminant function analysis yielded the right VMPFC as a secondary factor influencing PM performance. According to classical studies on the VMPFC, most cases with damage to this area show inappropriate social behavior, including emotionally insensitive social interaction, unexpected wandering, alcohol abuse, and confabulation. Despite these sociopathic psychopathological changes, higher-order cognitive functions including general memory performance are largely preserved. The somatic marker hypothesis proposes that damage to the VMPFC precludes the ability to use somatic signals that are necessary for guiding decisions in a positive direction (Bechara, Damasio, Damasio, & Anderson, 1994; Damasio, 1996). Sensitivity to appropriate contexts or cues for proper timing seem likely to depend on signals from autonomic (somatic) bodily responses.

Several other studies have indicated that the right VMPFC supports judgments of familiarity. Direct evidence from a neuroimaging study indicated that the right VMPFC is highly correlated with familiarity judgment (Umeda et al., 2005). Morris, Cleary, & Still (2008) revealed a relationship between recognition ratings and temporal characteristics of the skin conductance responses (SCR), supporting the idea that feelings of familiarity are indeed feelings, in that they stem from autonomic arousal. As another interesting finding, a PM training study for two brain-damaged cases demonstrated no marked improvements in PMC in a case with damage to the right VMPFC (T.K.), although another patient with damage to the medial temporal lobe (Y.O.) showed marked improvements with training (Umeda et al., 2006). These data suggest that cognitive function in the right VMPFC is not easily recovered with PM training. This appears reasonable if the area is correlated with processing regarding autonomic arousal. A recent neuropsychological study indicated that patients with damage to the VMPFC experience a faster subjective sense of time (overestimated and underproduced time intervals) compared to normal healthy controls (Berlin, Rolls, & Kischka, 2004). This may be more evidence that the VMPFC is highly correlated with PM retrieval.

In terms of the DMPFC as the third key factor influencing PM performance, a great number of studies have been reported. Regarding the area inside this region, located in the vicinity of the anterior cingulate cortex (ACC), many neuroimaging studies have suggested that this area is highly correlated with mentalising or theory of mind reasoning (Gilbert et al., 2007; Frith & Frith, 1999; Umeda, Mimura, & Kato, 2010). In contrast, regarding the area outside this region, many neuroimaging studies have reported involvement in PM (Burgess et al., 2001, 2003; den Ouden, Frith, Frith, & Blakemore, 2005; Hashimoto, Umeda, & Kojima, 2010; Okuda et al., 2007) or in multi-task coordination (Gilbert et al., 2007). Most of those studies involving PM have found activation in the rostral PFC (BA10), particularly for maintenance of intentions (Burgess et al., 2007) or sustained responses (Reynolds et al., 2009). Another study reported that recognizing the appropriate context to act ("cue identification"), which is similar to PMC, is associated with lateral BA10 activation accompanied by medial BA10 deactivation (Simons et al., 2006). Similar results were obtained in another study, with responses to targets under self-initiated and cued conditions yielding greater activity in the lateral and

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medial BA10, respectively (Gilbert, Gollwitzer, Cohen, Burgess, & Oettingen, 2009).

Of note is the finding that BA10 was included in eight of the twelve areas for discriminant function analysis in the present study, if we disregard the position (superior or inferior, right or left) in BA10. Identifying the exact role of BA10 in the present study is difficult. At the very least, our findings support the involvement of BA10 in PMC, but careful examinations of which parts in BA10 are activated during tasks must be examined in future neuroimaging studies (Gilbert et al., 2009; Simons et al., 2006). As pointed out by Burgess et al. (2007), rostral PFC (BA10) lesions typically do not cause widespread cognitive decline, even in traditional tests of frontal lobe functions. Burgess et al. presume that rostral PFC lesions cause impairments, for instance, in self-initiated multitasking (see "the gateway hypothesis"). Further closer scrutiny of the function of BA10 will provide novel insights into the neural substrates of PMC and related components.

To investigate the functional characteristics of PMC, we first compared neuropsychological test scores between "success" and "failure" groups. Significant differences between these groups were found only in total and orientation scores of the HDS-R, with both scores higher in the "success" group. Total and orientation scores of HDS-R are broadly used as diagnostic criteria for AD and other types of dementia, so these correlations suggest PMC as another potential measure to predict demented or pre-demented status. This also suggests that PMC is an integrated memory function, associated with awareness of the current status. The overall lack of significant differences between PM performance and most neuropsychological test was consistent with the previous finding showing that PMC is separable from functionings in other neuropsychological tests (Henry, Rendell, et al., 2007).

Some limitations to the present study must be considered. In the present study, the identification of lesion locations was based on independent careful visual inspections by two specialists. Considering recently developed methods, such as voxed-by-voxel lesion mapping, the present method is limited in preciseness for identifying lesion locations (Kinkingnéhun et al., 2007; Rorden & Karnath, 2004; Volle et al., 2008). Future studies should use a more reliable method to more precisely identify lesion locations. In addition, the degree of diffuse axonal injury (DAI) could have affected PM performance. In this study, we identified diffuse axonal injury in at least nine patients using the Susceptibility-Weighted Imaging (SWI) method in the MRI analysis. In order to see whether the presence of DAI affects the PM performance, we have compared the PM performance between the patients with and without DAI. The ratio of the patients with success in the PM task was .33 in the DAI group and .45 in the no-DAI group, and the difference was found to be non-significant ($\chi^2(1, N=74)=.08$, $p>.10$). However, identifying the presence and degree of diffuse axonal injury using the imaging method is limited as the effects of observable injury on behavioral performance remain unclear. Further neuropsychological study will be required with careful consideration of the effect by diffuse axonal injury.

In discriminant function analysis, three variables (right DLPFC, right VMPFC, and left DMPFC) accounted for 67.6% of the correct classification matrix. It is thus reasonable to infer that other brain areas beside the twelve areas we selected (e.g., thalamus) may also contribute to the matrix. Further neuropsychological investigations are required to identify other areas and completely account for PM performance. Moreover, the present study focused only on PMC, and neural substrates of RMC should be examined in the same manner. By understanding the neural bases for PMC and RMC globally, the neural mechanisms of PM will be illuminated. The present study for a large study population represents a first step toward progress in this research area.

Another limitation is concerned with the PMC–RMC division. Some recent models suggest that prospective memory retrieval consists of multiple processes. The preparatory attentional and memory processes (PAM) theory assumes that people initiate preparatory attentional processes directed at considering environmental events as potential targets for intention retrieval (Smith, 2010; Smith, Hunt, McVay, & McConnell, 2007). Preparatory attentional processes are assumed to draw on limited-capacity resources and can range from fully conscious strategic monitoring to preparatory attentional processes that are outside of focal awareness. On the other hand, the multiprocess theory posits that prospective memory would have adapted to rely on multiple processes for prospective memory retrieval (Einstein & McDaniel, 2008; McDaniel & Einstein, 2007). The theory assumes that the presence of a target event or cue can spontaneously initiate retrieval of the prospective memory intentions from memory even when no preparatory attentional processes are engaged (Einstein & McDaniel, 2010). Although the necessity of the preparatory attentional process for spontaneous prospective memory retrieval is still under debate, future neuropsychological studies should carefully examine the role of pre-attention in PMC.

Finally, from a clinical perspective, we should mention that the efficacy of PM rehabilitation is important for improving quality of life (QOL) in patients with brain damage (Umeda et al., 2006). Past studies have shown that PM training is effective in improving PM performance for patients with AD (McKitrick, Camp, & Black, 1992) and for brain-damaged patients (Sohlberg, White, Evans, & Mateer, 1992a, 1992b). Effective methods for achieving PM rehabilitation have remained contentious for over 20 years. The present findings may provide some clues to establishing appropriate PM rehabilitation programs depending on the damaged areas in the brain.

Overall findings from this study suggest that PMC, as timing-based spontaneous prospective memory retrieval, requires integrated memory function implemented by areas within the prefrontal cortex. The discriminant function analysis enabled us to understand the neural substrates of PMC to support the notion.

Acknowledgements

This study was supported by a Grant-in-Aid for Scientific Research (No. 21530770) from the Japan Society for the Promotion of Science (JSPS). We are grateful to the patients who participated in our study.

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Please cite this article in press as: Umeda, S., et al. Deficits in prospective memory following damage to the prefrontal cortex. *Neuropsychologia* (2011), doi:10.1016/j.neuropsychologia.2011.03.036