Knowing Your Lines but Missing Your Cue: Rostral Prefrontal Lesions Impair Prospective Memory Cue Detection, but Not Action-intention Superiority

Sharon Uretzky[1*] and Asaf Gilboa[2,3*]

Abstract

■ Prospective memory (PM) deficits are a common consequence of lesions to PFC, but their underlying neurocognitive mechanisms and processes are poorly understood. Here, we report on a patient, Z. P., who suffers from a chronic focal PM deficit, while other cognitive functions including memory are intact. His lesion involves right polar PFC (Brodmann's areas 10 and 9). Z. P. was very impaired on tasks that require detection of PM cues during an ongoing task. He was impaired regardless of whether the PM cues involved effortful or nearly effortless detection on the part of controls. By contrast, on tasks that tap the underlying (implicit) representations of intentions to perform an action, Z. P. showed normal patterns of intention superiority effects (ISEs) for to-be-performed actions and an inhibition effect for prospective actions after they had been performed. Thus, this is the first report of a neuropsychological dissociation between preserved privileged representation of prospective intentions and impaired detection of cues that support the opportune recovery of PM. Our data are compatible with the "gateway hypothesis" of rostral PFC, but also suggest there are components that are unique to PM and that remain intact after lesions to this region. ■

INTRODUCTION

Prospective memory (PM) is a form of memory which enables the performance of future actions at certain future times or future events (Harris, 1984). The use of this form of memory is common and pertinent to many realms in daily life.

Cognitive Mechanisms of Prospective Memory

PM depends on complex neurocognitive processes which often involve the functioning of multiple neurocognitive domains, such as retrospective memory and executive functions (Burgess & Shallice, 1997). However, neuropsychological studies have reported patterns of impaired PM despite intact functioning on domains considered critical for its performance, suggesting it also relies on certain unique and dissociable neurocognitive underpinning (West, McNerney, & Krauss, 2007; Bisiacchi, 1996).

There are two dominant theoretical approaches that describe the neurocognitive mechanisms underlying prospective remembering. One focuses on monitoring of the environment and cue detection (Einstein & McDaniel, 2005; Smith, 2003; Burgess & Shallice, 1997) and the other focuses on the internal representations of intention for action (Goschke & Kuhl, 1993). The former models focus on the kinds of processes that allow prospective actions to be performed at the appropriate times, whereas the latter models attempt to explain the manner in which prospective actions gain precedence over other representations to allow them to interrupt ongoing behavior.

Monitoring and Cue Detection

There are two primary models describing how cues associated with prospective intents activate PM representations. One model suggests that prospective remembering is enabled by a monitoring mechanism that is activated when an intention for action is created. This retention mechanism of the prospective intent requires attention and executive resources. It monitors the environment strategically until the target event for action execution is encountered. The prospective mechanism signifies the target event's presence (Smith, 2003; Burgess & Shallice, 1997) and inhibits the competing on-line action schema in order to enable execution of the prospective action schema (Burgess, Scott, & Frith, 2003).

A frequent empirical method to examine monitoring functioning in laboratory experiments is by using an ongoing task during which prospective targets periodically appear and should be responded to distinctively. For example, subjects perform an ongoing lexical decision task during which they are also required to respond every time

[1]National Institute for Rehabilitation of the Brain Injured, Haifa, Israel, [2]Haifa University, Mount Carmel, Haifa, Israel, [3]Rambam Medical Center, Haifa, Israel
*Equal contribution.

they identify a certain syllable (prospective target) inside the words on screen.

Research shows that adding the prospective task demands attention resources, and thus, results in a slower response time on the ongoing task (Smith, 2003).

A different account of prospective cue detection (Einstein & McDaniel, 2005) suggests that when intents for action are formed, an association between the action and the cue for action performance is encoded. When the cue representing the target event is identified, the association automatically activates the intention for action, which becomes conscious (Moscovitch, 1994). It is a reflexive direct retrieval operation that does not demand attentional resources. This theory mainly explains event-based rather than time-based PM.

Typical experiments examining this theory are similar to the abovementioned paradigm, in that subjects perform an ongoing task during which prospective targets may sporadically appear and should be responded to. The primary difference is that prospective targets, such as syllables, are not the primary focus of the ongoing task, which results in slower reaction times (RTs) during lexical decisions, as predicted by the active monitoring hypothesis. By contrast, when the targets are a salient part of the focus of the ongoing task (e.g., a word in the lexical decision task), spontaneous associative processes contribute more to the activation of the prospective intention and little cost in RTs is observed.

The "multiprocess theory" suggests that cue detection during prospective remembering relies, to different degrees, on both types of processes. The relative prominence of more controlled versus more automatic processes varies under different conditions depending on a variety of variables. Some of the variables are related to the character of the task (e.g., the distinctiveness of the target event, the type of processing necessary to identify it) and some to individual differences (Einstein & McDaniel, 2005; McDaniel & Einstein, 2000).

Intention for Action Representation

A second approach to PM focuses on the uniqueness of memory representation rather than on the prospective retrieval process. It has been suggested that representations of action intents within retrospective memory have an elevated activation level and, as a result, are more salient compared to other representations. This saliency mediates a privileged access to consciousness, which allows action intentions to be remembered prospectively and be executed in the future (Goschke & Kuhl, 1993).

The "intention superiority effect" (ISE) is a phenomenon which supports this theory. The ISE describes the findings that the processing of items in long-term memory, associated with a yet-to-be executed prospective intention, is faster compared with the processing of items from long-term memory that are not related to the intention (Goschke & Kuhl, 1993). In a typical experiment examining this phenomenon, subjects are asked to memorize two different "scripts," each comprised of a set of instructions to be performed in the future, and after learning them, are asked to perform only one. Before performing the script, they are given a lexical decision task containing words that appeared in both scripts. Although both scripts are memorized to the same extent, RTs for words associated with a prospective intention are faster than RTs for words not related to the prospective intention. This suggests an elevated activation level and resultant privileged processing for representations of the intention for action (Marsh, Hicks, & Bink, 1998). A related finding is that RTs for items associated with an already executed prospective intention are slower than RTs for items associated with nonprospective items in long-term memory, suggesting an inhibition of activation of performed actions (Marsh et al., 1998).

Neuropsychology of Prospective Memory

Most of the research into PM impairment has dealt with populations suffering from general cognitive decline, such as aging, dementia, traumatic brain injury, or multiple sclerosis (e.g., Kardiasmenos, Clawson, Wilken, & Walllin, 2008; Troyer & Murphy, 2007; Umeda, Nagumo, & Kato, 2006; Worthington, 1999). Deficits have generally been ascribed to attentional/executive dysfunction, which is usually ascribed to prefrontal cortex (PFC) or its connections with subcortical structures. However, because other cognitive domains that support PM are often also affected by these conditions, the specificity of the relationship to the prospective components could not be determined.

Neuropsychological case studies of patients with prominent PM impairment generally pointed to different aspects of PFC including medial PFC (Cockburn, 1995), orbitofrontal PFC (Worthington, 1999), or PFC nonspecifically (Bisiacchi, 1996). West et al. (2007) have implicated white matter and brain stem abnormalities, which could lead to a disconnection syndrome with a PM dysfunction. In some of these cases, PM impairment appeared alongside more general executive impairment (Worthington, 1999; Cockburn, 1995) and, in one case, alongside partial working memory (WM) impairment (West et al., 2007).

One prominent neuropsychological theory of PM specifically implicates the rostral PFC (roughly corresponding to Brodmann's area 10) as critical to maintaining intention over time and interference (Burgess, Simons, Dumontheil, & Gilbert, 2005). By this view, primarily supported by neuroimaging data, rostral PFC acts as a gateway between attentional functions related to "stimulus-independent" self-maintained thought (mediated by lateral rostral area 10) and "stimulus-oriented" attending (mediated by its medial aspect). PM is considered a prime example of a more general collection of functions, such as multitasking, that involves conscious switching between attending to the environment and attending internally to one's thoughts, goals, and intentions.

Neuropsychological studies of the cognitive mechanisms that characterize PM dysfunction have primarily focused on cue characteristics (e.g., event- vs. time-based PM) and cue detection deficits in general. To our knowledge, the distinction made in cognitive studies between monitoring and associative cue detection has not been examined in patients with focal lesions. Furthermore, although some neuropsychological studies demonstrated the distinction between explicit prospective and retrospective memory mechanisms (e.g., West et al., 2007; Umeda et al., 2006), the nature of representation of prospective intentions, as reflected by the implicit automatic mechanism of the ISE, has not been directly examined.

The present research describes a patient with lesions to rostral PFC in regions that correspond to Brodmann's areas 9 and 10, who suffers from a selective PM impairment while other executive functions, as examined by standard neuropsychological tests, are mostly intact. Its aim is to test possible dissociations within PM dysfunction between the processes and representation described above: (i) controlled monitoring, (ii) automatic associative retrieval, and (iii) increased activation of intention for action.

METHODS

Subjects

Case Description

Z. P. is a 41-year-old right-handed man. He has 17 years of education with degrees in civil engineering and business administration, which he completed after the injury. In 1984, at the age of 18, he was involved in a car accident and sustained a mild to moderate head injury. There was a brief loss of consciousness (duration not specified in his medical file). A CT that was performed after injury showed a dense right frontal fracture to the skull, with no other injury and no dural damage. He was hospitalized for 3 weeks and treated conservatively before being released. Three years after the accident, carnioplastic surgery was performed and the skull was reconstructed with silicone. An MRI which was performed for the purpose of the present study was interpreted by a neuroradiologist as normal save for the old right frontal fracture and the cortex under the fracture which was atrophied, involving right fronto-polar cortical regions (Figure 1). To better characterize the extent of atrophy and the cortical areas involved, we used a procedure based on Damasio and Damasio (1989). However, rather than the standard Brodmann's areas, we used the more refined Petrides and Pandya (1994) architectonic divisions for the frontal lobes (Stuss et al., 2002, 2005). Images were reoriented to the AC–PC plane, and the extent of atrophy was delineated. The delineation was then transposed onto a template.

In his everyday life, Z. P. suffers from a profound impairment in PM, which disrupts his functioning and quality of life significantly. For example, throughout the past 20 years, he was unable to maintain a stable employment because he would fail to attend meetings and fail to perform tasks on time. He is currently employed as a freelance lecturer of business administration, but reports difficulties returning to the main theme of a lecture after replying to questions or other digressions. Following cognitive rehabilitation, which he recently sought, his lectures are now more coherent and less associative, although he still experiences some difficulties. While driving, he has trouble getting to new destinations because he forgets to perform critical turns and finds himself driving by known, automatic driving tracks, despite being able to recall the new route in retrospect. While cooking, he frequently forgets to turn off the gas on time. He might also start activities and forget to finish them (e.g., boiling water for tea but forgetting to prepare it). On most of these occasions, it appears that Z. P.'s difficulty is performing the actions on time, rather than the actual memory of the to-be-performed action.

Z. P. is sometimes able to remember a prospective task when the retrieval cue is conspicuous and when the associative relationship between the cue and the response does not require generalization. For example, he was asked to fast before a blood test and explicitly created an associative relationship between his refrigerator and his intention not to eat. He was able to fast at home, but when passing near a pizzeria on his way to the clinic for the blood test, he bought pizza, failing to generalize the cue–intention association. Z. P. also does not consider "prospective consequences" of his acts, which may be related to his associative generalization difficulty. For example, he could lend a book to someone without remembering when lending it that he would need it himself later in the day.

In addition to his prospective difficulties, Z. P. describes difficulties in multitasking (such as planning his daily schedule within a reasonable time), in prioritizing tasks, and in efficiently planning task performance. These difficulties become more prominent when he is overburdened and under time pressure.

After forgetting to perform a prospective task, Z. P. sometimes experiences an awkward sensation which he interprets as a signal that he forgot to do something. Attempting to recall what it was that he forgot is only occasionally successful.

A formal neuropsychological assessment was administered 3 years prior to the present study when Z. P. was 38 years old (see Table 1). Intellectual ability was in the average to high-average range. The only performance index outside the average range was the processing speed index, which was borderline to low average. Slowed psychomotor speed was also noted on the Purdue Pegboard, which was low average.

Retrospective memory performance was compatible with the general intellectual performance and was largely in the average to high-average range. An executive function difficulty was not detected in relevant formal tasks, although clinical observations suggested he had difficulty in organization and planning in the initial stages of processing.

Z. P.'s prospective impairment was clinically assessed by the Prospective and Retrospective Memory Questionnaire

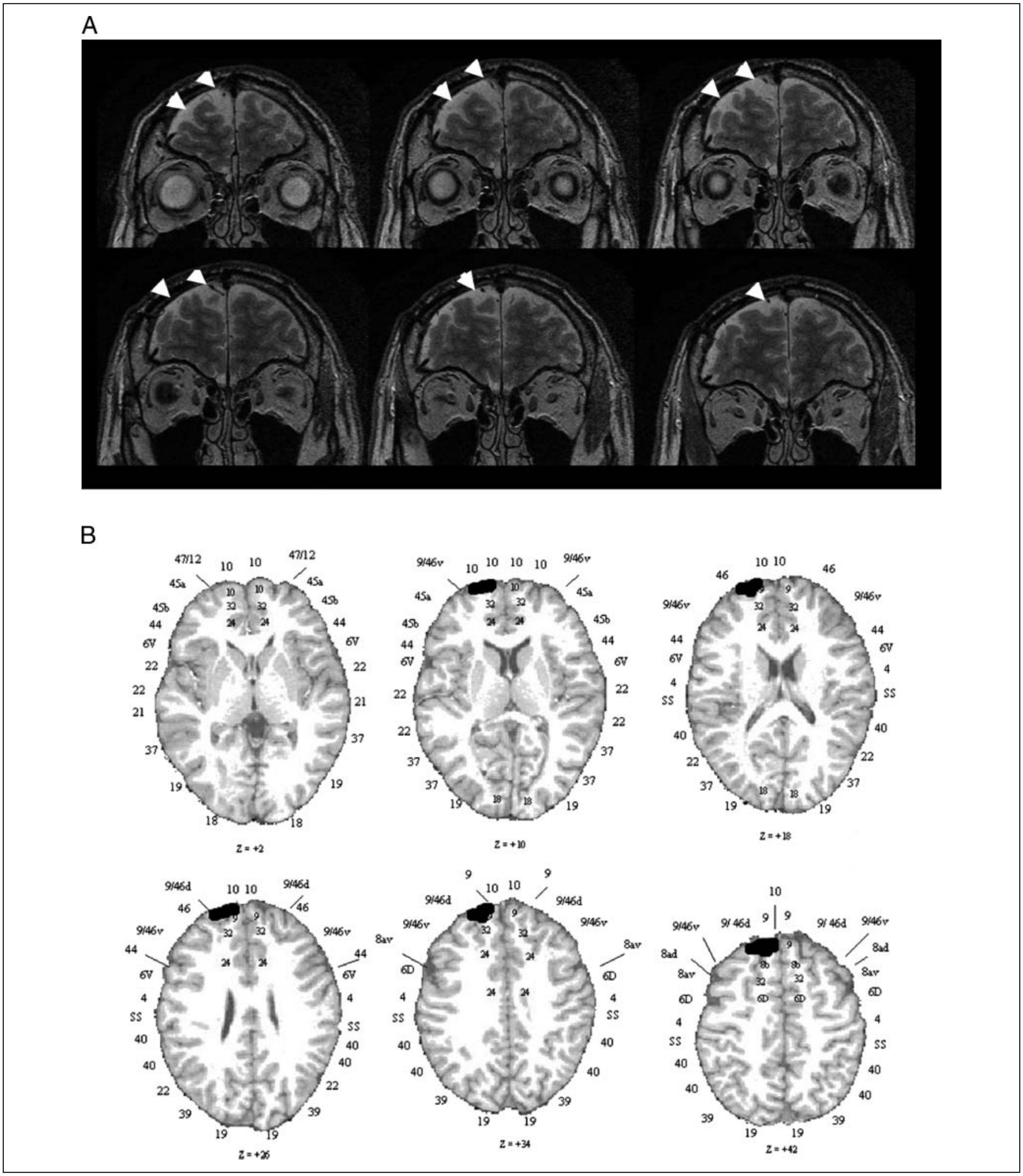

Figure 1. Coronal T2 magnetic resonance images showing the right fronto-polar atrophy (white arrows) in Z. P. (A). The extent of atrophy was delineated on a template brain according to Petrides and Pandya's (1994) cytoarchitectonic division using a system developed by Stuss et al. (2002). See text for details.

(Table 1). On the retrospective memory subscale, his score was average (t = 53), confirming neuropsychological test performance. He had a severely impaired score on PM (t = 11), reflecting a significant difference between the prospective and retrospective memory, with less than 1% of the population expected to demonstrate such a difference (Crawford, Henry, Ward, & Blake, 2006). Another formal measure that indirectly assesses PM is the Auditory Consonant Trigram (ACT), which unlike other standard measures of WM, requires maintenance of information

Table 1. Z. P.'s Performance on Standard Neuropsychological Tests

Cognitive Domain	*Test*	*Score*
General intellectual	WAIS-III	
	VIQ	121[a]
	PIQ	104[a]
	FSIQ	113[a]
	WMI	99[a]
	PSI	79[a]
	POI	109[a]
	VCI	122[a]
Memory	WMS-III	
	Immediate Memory index	108[a]
	General memory index	108[a]
	Single trial learning	72[b]
	Memory retention	95[b]
	PRMQ	
	Prospective	**11**[c]
	Retrospective	53[c]
Attention/executive	WCST	
	Categories (6 achieved)	0.4[d]
	Trials to 1st category	0.14[d]
	Perseverative errors	0.26[d]
	Category Test (Reitan)	0.23[d]
	Spatial span	8[e]
	Letter–number sequences	8[e]
	Digit span	9[e]
	Auditory Consonant Trigrams	**−3.9**[d]
	PASAT	−0.45[d]
Motor speed	Purdue Pegboard	
	R	−0.95[d]
	L	−1.08[d]

Bolded scores represent a significant impairment.

FSIQ = Full Scale Intelligence Scale; PASAT = Paced Auditory Serial Addition Test; PIQ = Performance Intelligence Quotient; POI = Perceptual Organization Index; PRMQ = Prospective Retrospective Memory Questionnaire; PSI = Processing Speed Index; VCI = Verbal Comprehension Index; VIQ = Verbal Intelligence Quotient; WAIS-III = Wechsler Adult Intelligence Scale III; WCST = Wisconsin Card Sorting Test; WMI = Working Memory Index; WMS-III = Wechsler Memory Scale III.

[a]Standard score.

[b]Percentile.

[c]*t* score.

[d]*Z* score.

[e]Scaled score.

over a period of time filled with interference, which prevents rehearsal (Burgess et al., 2005). Z. P. was profoundly impaired on the ACT (0 points), in sharp contrast to his average performance on regular WM tasks, including the PASAT and span tasks.

Control Subjects

Eight healthy control men who were matched to Z. P. in terms of age (±5 years) and education (±2 years) served as control subjects. Their ages ranged between 37 and 46 years old (average age = 40.6 years), and they had between 15 and 17 years of education (average = 16.1 years).

All subjects were born in Israel and were native speakers of Hebrew. They did not suffer from any neurological or psychiatric illness or had any learning disability. All had normal or corrected-to-normal vision.

Procedure

The experimental procedures consisted of two basic paradigms designed to investigate activation of prospective intentions and detection of prospective cues, respectively, as described below.

Experiment 1: activation of intentions. MATERIALS. Experiment 1 had two parts which involved the presentation of four Hebrew scripts, two for each of its parts. Each script was composed of a title (e.g., "Meal preparation") and of five short action sentences that included a gerund, a connector, and a noun (e.g., "To cut the tomatoes"). The scripts were semantically unrelated.

In each of the two experimental sections, there was a lexical decision task composed of three kinds of items—(1) Twenty words that appeared in the two previously learned scripts. Half of those words were gerunds and half nouns. (2) Twenty new semantically unrelated words. Those words were composed of 10 gerunds and 10 nouns with similar length to those that appeared in the scripts. (3) Forty pronounceable nonwords. Thus, the probability for a positive answer during the lexical decision was 50%.

To practice the lexical decision task, 20 additional stimuli were presented: 10 words and 10 nonwords.

Words appeared in a predetermined pseudorandom order which was set through a random number generator with the proviso that two words from the same script never appeared consecutively. Once the pseudorandom order was determined, all subjects saw the words in the same order.

PROCEDURE. The experimental procedure design is based on the original paradigm of Marsh et al. (1998). Subjects were asked to memorize two pairs of scripts, each pair in a different part of the experiment. Afterwards, they were asked to perform only one of the scripts from each pair they have learned.

Before the beginning of the experiment, the subjects were given instructions for the lexical decision task and

20 stimuli were practiced. If there was difficulty understanding the task, it was possible to repeat the practice. Subjects were asked to press one key for "yes" when the string of letters they saw presented a Hebrew word and a second key for "no" when the string of letters was not a word. They were asked to respond as fast and as accurately as possible. Throughout the lexical decision task, the words yes and no appeared at the bottom of the screen, corresponding to the key location, to minimize WM demands and errors in key to response mapping.

In each part of the experiment, subjects were presented twice with two consecutive scripts. The order of script presentation was counterbalanced so that the to-be-performed script appeared either first or second during learning in the first and second parts of the experiment. Script presentation began with a script title followed by script sentences, which were added consecutively every 10 sec until, finally, the whole script appeared on the screen. This was followed by an additional 30-sec presentation of the complete script on screen.

After both scripts appeared on the screen twice, subjects were requested to write down the two scripts in the order of their appearance. If they did not recall the scripts precisely they were presented with an additional single learning sequence of both, and so on, until perfect recall was attained.

As soon as the learning criterion was achieved, subjects saw a three-digit number on the screen and were asked to count aloud backwards by 3s. This was done to prevent rehearsal of the scripts during the short delay period. A tone signified the end of 45 sec of counting, and a message appeared on the screen stating which script is to be performed and which script would not be performed.

In the first part of the experiment, subjects heard a 500-msec preparatory tone immediately after they learned which script was to be performed, and were administered the lexical decision task. Lexical decision trials consisted of a word stimuli which remained on screen until a response was made, followed by a 200-msec delay before the next trial. At the end of the lexical decision task, subjects were taken to a nearby room where they performed the prospective script while verbally recounting the script.

In the second part of the experiment, the procedure was similar, except that the prospective task was performed immediately after subjects had learned which task was to be performed and the lexical decision task followed performance of the prospective script.

Throughout the experiment, the instructions were presented written on screen and were accompanied by an oral explanation. Subjects were informed in advance at the beginning of each experimental part about the expected procedure.

Experiment 2: strategic vs. automatic detection of prospective cues. MATERIALS. The experimental procedure design is based on the original paradigm of Einstein and McDaniel (2005).

The stimuli in both experimental sections consisted of word pairs—half of which were semantically related (e.g., tango–flamenco), and half were unrelated (e.g., tornado–pistol). The first experimental section consisted of 128 pairs of words in each of its two parts. The second section consisted of different words, 124 pairs in each of its two parts. Each of the two experiments consisted of four buffer pairs. In the first section (which included altogether 252 pairs + 4 buffer pairs), each word appeared four times: twice as a member of a related pair and twice as a member of an unrelated pair. In the second section, (included 244 pairs + 4 buffer pairs), each word appeared once. The order of appearance of the pairs of words in each section of the experiment was randomized, but was kept constant across subjects. Prospective target stimuli (see below) appeared in fixed experimental trials (numbers 30, 60, 90, 120).

In addition to the experimental stimuli, there were 16 pairs of related and unrelated words which were used for practice (6 pairs used as first practice before experiment, and 10 pairs as second practice before experiment and before each of the two prospective parts). For training before prospective trials, one of the words from the 10 practice pairs was replaced by a prospective target word. Practice words were not related to the semantic categories that appeared in the experimental tasks.

PROCEDURE. During both sections of the experiment, subjects were consecutively presented with word pairs and were asked to press one key for "yes" if they thought the words belonged to the same category and a second key for "no" if they were from different categories. The prospective task during the second part in each section involved pressing the spacebar whenever a target cue appeared in addition to the ongoing categorization task. During the first section, the prospective target cue was a word, which is considered a "more focal" cue because words are the focus of attention in the ongoing task. During the second condition, a single syllable within a word was used as the target cue. It is considered a "less focal" target cue because syllables are irrelevant to the ongoing task (see Einstein & McDaniel, 2005 for a discussion).

Before beginning the experiment, subjects practiced the ongoing categorization task twice—once with no speed limit, and the second time they were instructed to respond as accurately and as fast as possible. After responding to each pair, a feedback regarding their response time and accuracy in performance appeared on screen. It was possible to perform more practice rounds if necessary.

After the practice, subjects began the first categorization task, which was identical to the practice phase, but without the feedback and with different categories. In its second half, they again performed a categorization task, but this time also had to monitor for the appearance of a more focal target cue (the word "cabinet" in Hebrew) and press the spacebar every time it appeared, and then continue with the ongoing categorization task. They were also asked to respond to the target word even if noticing its appearance late (a few pairs of words after its appearance). A practice trial for the prospective part of the task was administered prior to the onset of the actual task. Subjects who did not respond to the target word performed the practice again, until a correct performance was achieved.

The second section of the experiment also had a baseline categorization part and a second categorization part, which also included a prospective task. However, the prospective target was a syllable within a word—"lit." A practice trial was provided before the prospective task, as in the first section. After completing the experiment, subjects were asked to recall the prospective target stimuli to verify they could retrospectively recall their prospective tasks.

In each section in the experiment, the prospective cue appeared four times. In the first section, the more focal cue was a word and, therefore, resulted in the presentation of all words four times. In the second section, every word appeared only once, as the cue is a syllable and is less focal. A repetition of words in this section would have created an association between the word and the cued syllable and, therefore, spoil the less focal quality of the syllable. The number of words within each ongoing task was determined by the need to counterbalance the different categories.

During all parts of the experiment, word pairs appeared on the screen until a response was made. Mapping of keys to responses (yes/no to left/right) appeared at the bottom of the screen throughout the experiment.

RESULTS

To test for differences between conditions within the control group, we used Friedman nonparametric ANOVA followed by Wilcoxon post hoc test in order to examine differences between specific conditions. To compare the performance of Z. P. to that of the control group, we conducted a modified *t* test which treats the score of the individual patient and the scores from the small comparison group as a sample (i.e., a sample statistic) rather than as a "population" or a parameter (Crawford & Garthwaite, 2002; Crawford, Howell, & Garthwaite, 1998). Specifically, the formula uses the standard deviation of the control group and treats the single subject as a group of $n = 1$ in the following manner:

$$t = (X_1 - X_2)/S_2 * \sqrt{((n_2 - 1)/n_2)}$$

Where X_1 is the individual's score, X_2 is the mean of the normative sample, S_2 is the standard deviation of the normative sample, and n_2 is the n of the normative sample (in this case, 8).

Automatic Activation of To-Be-Performed Actions and Deactivation of Performed Actions

In the first part of the experiment, where the prospective task was to be performed after the lexical decision task, four repetitions of the scripts were required for Z. P. to reach the criterion of errorless recall of the scripts. Four of the controls only needed the minimum two repetitions, three needed three repetitions, and the remaining control needed five repetitions to reach the criterion. After completing the lexical decision task, Z. P. could not remember which of the two tasks he was to perform, although he could still remember the action sequences themselves perfectly well. Thus, on the retrospective aspect of the experimental task, Z. P. displayed intact retention of the information, in accordance with his standard neuropsychological test scores. However, he also presented with slowed acquisition compared with controls, which is not evident in his neuropsychological assessment and may be related to the prospective nature of the encoding task. His failure to remember which of the two tasks he was to perform is also difficult to interpret as it may be due to his PM deficit and the interfering task which followed the learning phase (see discussion of the role of interference in PM below).

His RT profile during the lexical decision, on the other hand, did not differ from that of controls (Figure 2). Z. P. showed a facilitation effect of 56 msec for old words that belonged to the to-be-performed (prospective) script compared with old words belonging to the nonprospective script (roughly 8% facilitation). Controls' RTs also differed across word types (Friedman nonparametric ANOVA, $\chi^2 = 9.15, df = 3, p < .05$) and showed an average

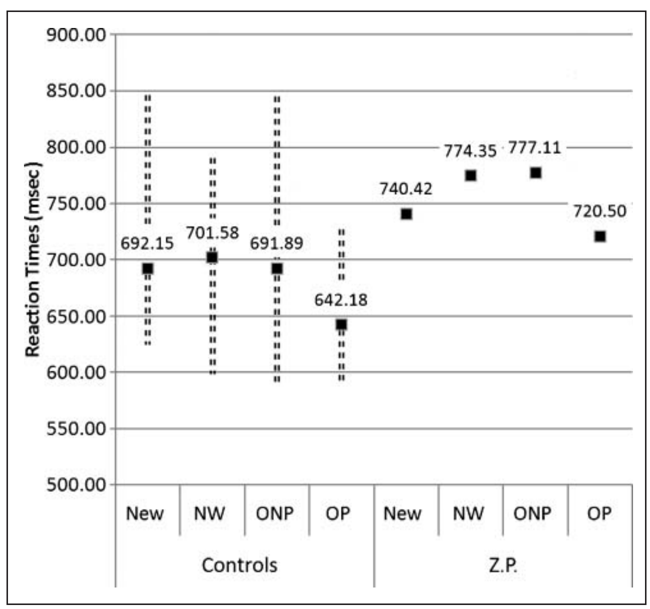

Figure 2. Mean RTs of Z. P. and controls during lexical decision for different word types prior to performing a prospective task. NW = nonwords; ONP = old nonprospective; OP = old prospective. Double-dashed lines represent controls' score range.

of 50 msec facilitation effect (roughly 7% facilitation), which was significant (Wilcoxon test comparing old prospective and old nonprospective $Z = -2.38$; two-tailed $p < .05$), replicating the results of previous studies. Z. P.'s facilitation effect did not significantly differ from that of controls [$t(7) = 0.16, p > .05$]. Thus, stimuli belonging to the prospective script were more rapidly processed by controls and by Z. P. than stimuli that were similarly studied but did not belong to a to-be-performed script.

An unexpected feature of the results was that Z. P.'s RTs to new words was 37 msec faster than his RTs to old nonprospective words, which suggests that some of the facilitation effect for to-be-performed stimuli might be due to inhibition of familiar stimuli that are not to be performed. Among controls, too, there was a great variability in the RT difference between new and old nonprospective stimuli, which ranged from 46 msec faster for old nonprospective to 35 msec faster for new words (which is essentially the same pattern displayed by Z. P.). There was no statistically significant difference between Z. P. and controls on the RT difference between these two conditions [$t(7) = 1.4$, $p > .05$], but the overall pattern still suggests that the advantage of to-be-performed representations may reflect mechanisms that are more complex than simple facilitation.

During trials where the script was performed prior to the lexical decision task, Z. P. again needed four repetitions to reach a criterion of errorless reproduction of the scripts in writing. Four of the controls needed the minimum two repetitions and four controls needed three repetitions. This time, Z. P.'s memory performance was outside the range of controls, which may reflect the added effect of fatigue to his already slowed rate of acquisition. Fatigue might also explain the greatly increased latencies of decisions to reject nonwords during the lexical decision task (Figure 3). This slowed reaction to nonwords was not driven by outliers, and reflects an unusual pattern of performance on this task compared with the first task, which we cannot explain.

In terms of the RTs to old stimuli that belong to the already-performed prospective task, Z. P. showed the expected slowing compared with old words that never belonged to a prospective task (143 msec, roughly 23% slowing). Controls' performance differed across word types (Friedman nonparametric ANOVA, $\chi^2 = 10.35$, $df = 3$, $p < .05$), but unlike Z. P., they did not consistently show the expected slowing of responses to already performed stimuli (Wilcoxon test comparing old prospective and old nonprospective $Z = -1.12$; two-tailed $p > .05$). Numerically, four controls showed slowing of responses to already-performed prospective stimuli, one showed a prospective facilitation effect and three showed no difference between the different types of stimuli. This pattern constitutes only partial replication of previous reports with larger samples in that performing a prospective task appears to largely eliminate the facilitation effect associated with prospective intention, but only some of our subjects,

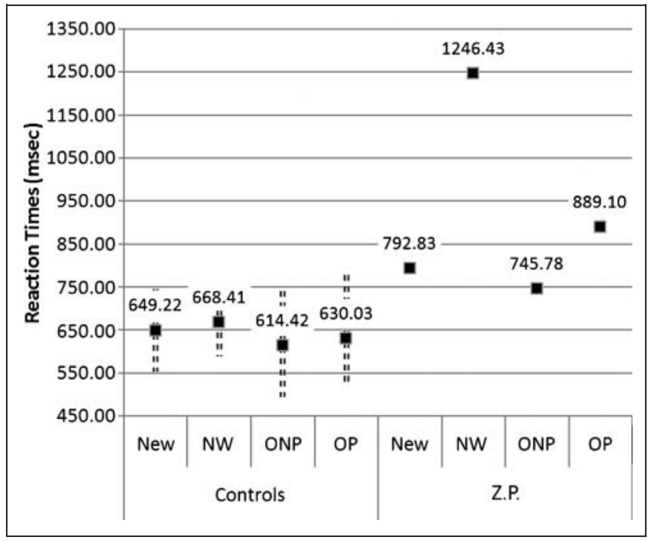

Figure 3. Mean RTs of Z. P. and controls during lexical decision for different word types after performing the prospective task. NW = nonwords; ONP = old nonprospective; OP = old prospective. Double-dashed lines represent controls' score range.

in fact, show the expected inhibition. The difference between prospective and nonprospective stimuli presented by Z. P.'s was significantly larger than that presented by controls [$t(7) = 2.99, p < .05$], as even the control with the largest effect showed a 79-msec slowing (roughly 13%).

To conclude, both Z. P. and controls showed the facilitation effect reported in the literature during the processing of stimuli that belong to a prospective task, compared with previously encountered stimuli that do not have a prospective status. By contrast, the reported inhibition effect (IE) of processing of stimuli associated with already-performed intentions was evident in Z. P. but only partially replicated in our controls. Informal observation suggested that two control subjects were aware of the fact that the stimuli in the lexical decision task came from the prospective task, an awareness that may have affected their performance. One of them showed a large facilitation rather than IE and the other showed no difference between the prospective and nonprospective stimuli.

Controlled Monitoring of Prospective Cues

The second set of tasks was designed to examine the contribution of automatic and controlled conscious monitoring to detection of cues associated with a prospective task. The critical measure in both tasks was the cost in RT when performing a category classification task while having to monitor for prospective cues compared with the absence of a prospective task. There were two types of prospective cues: in more focal cues, there is a high correspondence between the prospective cue and the ongoing task. Monitoring for more focal cues is thought to require little cognitive resources (i.e., expected small cost in RT). By contrast, in less focal cues, there is little such correspondence, and monitoring for prospective cues under this condition is thought to rely more heavily on controlled processes which require cognitive resources. Cost was calculated as the percent increase in RTs from the no prospective to the prospective condition.

Six of the eight controls detected all four more focal targets within the allowed delay of one item, and the other two detected three of the four targets. On average, RT to press the spacebar for the more focal targets was 2097 msec. Z. P. did not detect any target within the allowed lag, and only detected one target at a lag of three items, 12 sec after it appeared.

All four less focal targets were detected by six of the controls within the allowed one-item lag, whereas the other two controls detected three and two targets, respectively. The average time it took to respond to the prospective cue was 2208 msec. Z. P. did not detect any of the less focal targets either within the allowed time or at longer delays. All subjects, including Z. P., successfully remembered both more focal and less focal targets after performing the relevant tasks.

Figure 4 presents the RTs for both types of prospective cues compared with their respective no-prospective task baselines. Controls were faster than Z. P. on all conditions by 30% on average. Note, however, that there was considerable variation among the controls in overall RT, such that the slowest control was, on average, only about 10% faster than Z. P., and even slower than him on the prospective less focal task, so we believe RT profiles can be meaningfully discussed.

Importantly, although all controls showed the expected pattern of RT cost associated with the addition of a prospective task, there was considerable variation in the magnitude of this cost. RT cost variation was reflected both within each type of task, and in cost increase across the different tasks (“more focal” vs. “less focal”). This finding

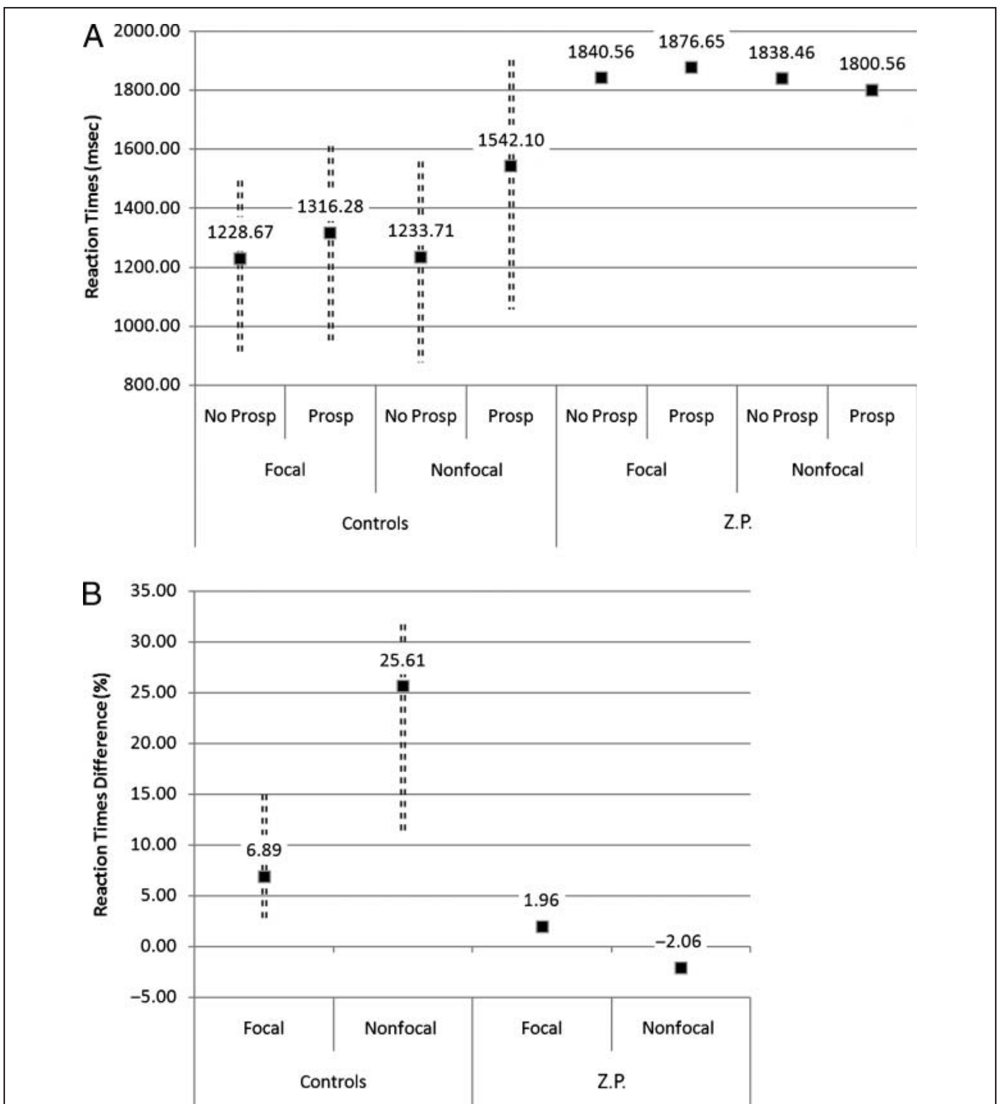

Figure 4. Mean RTs of Z. P. and controls during category classification with focal and nonfocal prospective cues (A), and differences between baseline and prospective conditions (B).

is compatible with McDaniel and Einstein's (2000) hypothesis regarding the influence of individual differences (in interaction with task related factors) on the extent of use of monitoring versus associative processes when accomplishing prospective retrieval.

In controls, the cost in RT on the category task when searching for the more focal prospective cue was 6.89%, and for the less focal prospective cue was 25.61%, which reflected a significant increase compared to the no-prospective cue condition in both cases [$t(7) = 2.98$, $p < .05$ and $t(7) = 6.73$, $p < .01$, respectively]. The cost increases in the two paradigms reflected the predicted significant increase in RT when the cue is outside the focus of attention compared with more focal cues [$t(7) = -3.54$, $p < .01$]. Z. P., on the other hand, showed no significant changes in RTs between prospective and nonprospective conditions. He presented with a 2% increase in RT for the more focal cues, which was not significantly different from controls' [$t(7) = -0.86, p > .05$] and a 2% decrease for the less focal cues, which was significantly different from controls' cost [$t(7) = -4.26, p < .01$]. Note that, in both cases, he did not detect any of the targets. There was no effect of prospective tasks on error rates either for controls or for Z. P. Error rates were low and hovered around 10%.

Note that, in both conditions of this experiment, the prospective stimuli appeared on the second part of the task. RT increases among controls in the prospective parts could therefore be interpreted as a result of fatigue build-up (Smith, 2003). However, Z. P., who failed to detect the prospective targets, did not show fatigue-related increases in RT as would be expected by this interpretation. Moreover, the RT increases in controls were greater for the attentionally more demanding task, suggesting that RT increases are the result of recruiting attentional resources in order to detect the prospective cues. Finally, findings from similar experiments (Einstein & McDaniel, 2005), in which counterbalancing for the detection of prospective stimuli was performed, also do not support the fatigue interpretation.

Dissociation between Automatic Activation Processes and Controlled Monitoring

To examine whether there is a dissociation between automatic activation of intentions which appeared to be preserved in Z. P. and controlled monitoring of the environment for prospective cues, we compared Z. P.'s ISE reflected by the facilitation of RT's on the lexical decision task and his RT cost for less focal prospective cues, when both scores were expressed as *Z* scores relative to controls' performance (Crawford & Garthwaite, 2002). His *Z* score for the lexical decision facilitation effect was 0.42 and for the less focal cue monitoring was −3.94, so that when applying the Revised Standardized Difference Test (Crawford & Garthwaite, 2002), the difference between the two scores was significant [$t(7) = 2.61$, $p < .05$]. As described above, his facilitation score for prospective stimuli did not differ from that of controls, whereas his cost score for monitoring less focal targets was significantly lower than that of controls, suggesting Z. P.'s performance fulfills the criteria for a classical dissociation.

DISCUSSION

The present study reveals a neuropsychological dissociation between preserved privileged representation of prospective intentions and impaired detection of cues that support the opportune recovery of PM in a patient with circumscribed fronto-polar lesions. Specifically, Z. P. presented with a normal ISE for to-be-performed prospective intentions, indistinguishable from that of controls in the present study and compatible with previous reports in the literature. Z. P. also demonstrated a strong IE for already-performed prospective intentions, which replicates previous studies with this paradigm but was only partially seen in our controls. By contrast, Z. P. was impaired on all aspects of cue monitoring and detection. When prospective retrieval cues were in the focus of ongoing activity, controls detected almost all of them. The addition of a prospective task had a significant but small effect on their RTs for the ongoing task. Contrary to controls, Z. P. was unable to identify any of the more focal prospective cues on time. His performance on the ongoing task was also unaffected by the addition of the prospective task, suggesting he was not recruiting cognitive resources in an attempt to compensate for his difficulty. Monitoring and detection of prospective cues outside the focus of ongoing activity involved even more effortful processing in controls as reflected by a significant increase in RTs for the ongoing activity and by a moderate drop in detection of cues in some subjects. By contrast, Z. P.'s ongoing activity was unaffected by the addition of a prospective task and he was unable to detect any of the cues. Importantly, on both tasks, Z. P. had no difficulty telling what the prospective cues and task were when directly questioned after the task was over.

Z. P.'s lesion and cortical atrophy involve fronto-polar regions on the right (corresponding to Brodmann's areas 10 and 9). Rostral PFC is a multimodal associative cortex which is considered by some to be the apex of a hierarchical functional prefrontal cortical system. This system is designed to guide behavior under conditions where no automatic or well-established course of action is available or under conditions where such automatic action schemata need to be overcome (Burgess et al., 2005; Fletcher & Henson, 2001; Christoff & Gabrielli, 2000; Grafman, 1995). This function could be achieved through the focus of attention to internally generated representations and plans of action (Christoff & Gabrielli, 2000) or through efficient switching between different representations (Burgess et al., 2005; Fletcher & Henson, 2001). Most relevant to the present study is Burgess and colleagues' suggestion that fronto-polar cortex plays an important role in PM by biasing the relative influences on behavior of stimulus-oriented and stimulus-independent attention and thought. PM tasks require the maintenance of delayed intentions while performing ongoing tasks, which prevent the continuous rehearsal of intentions. In Z. P.'s case, it is obvious that the system responsible for internal representations of prospective actions is intact, both in terms of retention of these plans and in terms of assigning them with privileged activation, which should allow them precedence in terms of selection for action. He is also able to perform ongoing tasks adequately, suggesting his stimulus-bound alertness and behavior are intact as well. He seems to have difficulty with efficiently monitoring the ongoing task for prospective cues and switching attention between the task and his inner prospective representation.

Moreover, Burgess et al. suggest that the critical aspect associated with performance of prospective tasks compared with regular working memory tasks is the existence of a distracting task between encoding and the need to perform the task. The maintenance and manipulation functions of WM are subserved by more posterior dorsolateral PFCs (e.g., Smith & Jonides, 1999; Petrides, 1996), which are intact in Z. P. In this respect, his overall intact ability on standard neuropsychological WM tasks is in sharp contrast with his absolute failure on the ACT. The latter differs from regular WM tasks, in that a backward counting distracting task is inserted between encoding of the trigrams and their retrieval. This is exactly the type of task that would require the intact functioning of polar PFC.

Z. P.'s failure on cue detection when the cue was in the focus of attention is surprising. His subjective reports suggest that he is sometimes reminded of prospective tasks when confronted with a prospective retrieval cue in his daily life. It was thus expected that the appearance of prospective cues as stimuli in an ongoing task would trigger his prospective intention through direct association. Controls' performance may provide a clue as to Z. P.'s failure on this task. Although in the more focal condition the stimuli for the ongoing task and for the prospective task were physically the same, controls showed a small but significant RT increase for the prospective condition. This increase suggests that processing a word as a prospective cue still required a shift from stimulus bound attention (focusing on semantic associations) to stimulus-independent thought (focusing on stimulus–planned action association), which Z. P. was unable to do. An important implication of this is that at least some attentional resources may always be required for prospective retrieval, as proposed by Smith (2003) (but see Einstein & McDaniel, 2005, for contradictory results). It may be that Z. P.'s sporadic successes in performing daily prospective tasks also depend on residual attentional abilities, contrary to his introspective reports of spontaneous activation. One interesting possibility is that his intact ISE (see below) may support directing of attention to internal representations of prospective tasks when there is little competition for attentional resources.

The ISE is interpreted as the accruing of heightened activation for to-be-performed declarative representations over those that have no action-related significance (Marsh et al., 1998; Goschke & Kuhl, 1993). Our results suggest that the ISE for the to-be-performed task might, in some cases, be accompanied by an IE over actions that are not to be performed, as demonstrated by slowed RT for old nonprospective items compared with new items, in Z. P. and two of our controls. Because memory for both scripts was the same, this might reflect a complementary mechanism which supports the distinction between action-relevant and action-irrelevant representations. Importantly, the fact that Z. P. shows intact ISE and IE implies that these mechanisms are independent of the function of the prospective cue monitoring mechanism. Anatomically, the memory representations of prospective tasks and cues are mediated by medial temporal lobe (MTL) structures, as suggested by Z. P.'s ability to retrospectively recollect the tasks and their associated cues. The preferential relative activation of cues associated with to-be-performed actions or inhibition of cues associated with already-performed actions are unlikely to be mediated by the MTL, which is considered a "stupid" memory structure (Moscovitch, 1994). ISE and IE are likely the product of executive mechanisms, mediated by prefrontal regions other than the rostral PFC region, which appears to take part in conscious controlled processes. One candidate region that may be involved in such functions is medial posterior orbito-frontal cortex (OFC). This region is critical in signifying the behavioral relevance of stimuli in the environment as part of the brain's reward system through representations of stimulus–reward associations. OFC may affect the relative activation of posterior neocortical representations through its subcortical connections with the ventral striatum, substantia nigra, and thalamic nuclei. There are data to suggest that the influence of OFC on behavior occurs at a preconscious level (Gilboa, Alain, He, Stuss, & Moscovitch, 2009; Gilboa, Alain, Stuss, Melo, Miller, & Moscovitch, 2006; Gilboa, 2004; Schnider, Valenza, Morand, & Michel, 2002). One influential theory suggests that this influence is related to the representation of current behavioral relevance of stimuli (Schnider et al., 2002), in accordance with the characteristics of ISE and IE in the present study. Future studies should examine whether ISE and IE depend on the functions of this prefrontal region.

It is noteworthy that despite intact ISE and IE, Z. P. fails on all aspects of PM tasks. This raises questions as to the unique functional contribution of these mechanisms to PM. Thus, ISE/IE mechanisms support or facilitate PM functioning but are not sufficient for it. On average, normal controls show the ISE effect quite consistently as seen in the present study and in previous research using this paradigm (Marsh et al., 1998). By contrast, the IE effect was much less consistently demonstrated. One possibility is that laboratory-based tasks can be performed without the contribution of preconscious mechanisms, for example, through reliance on conscious attentional mechanisms (mediated by rostral PFC). For example, despite the distracting task, two subjects reported being consciously aware of the presence of prospective stimuli, which is known to disrupt implicit processes (Lustig & Hasher, 2001). By contrast, in everyday life, the delay between encoding of prospective task and their performance can be longer and filled with more engaging "distracting" tasks, which make a continuous conscious representation of prospective cues less likely. Under these conditions, ISE/IE processes are more likely to be necessary for increasing the saliency of the prospective cue and the ability to identify it appropriately, but are not sufficient to support PM. In Z. P.'s case, the ISE/IE mechanisms may account for his partial ability to identify prospective cues in daily life and for his subjective uneasy sense of having missed a prospective task but being unable to retrieve what it is.

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Reprint requests should be sent to Asaf Gilboa, Psychology Department, Haifa University, Mount Carmel, 31905, Israel, or via e-mail: agilboa@psy.haifa.ac.il.

REFERENCES

Bisiacchi, P. S. (1996). The neuropsychological approach in the study of prospective memory. In M. Brandimonte, G. O. Einstein, & M. A. McDaniel (Eds.), *Prospective memory: Theory and applications* (pp. 297–317). Mahwah, NJ: Erlbaum.

Burgess, P. W., Scott, S. K., & Frith, C. D. (2003). The role of the rostral frontal cortex (area 10) in prospective memory: A lateral versus medial dissociation. *Neuropsychologia, 41,* 906–918.

Burgess, P. W., & Shallice, T. (1997). The relationship between prospective and retrospective memory: Neuropsychological evidence. In M. A. Conway (Ed.), *Cognitive models of memory* (pp. 247–272). Hove, UK: Psychology Press.

Burgess, P. W., Simons, J. S., Dumontheil, I., & Gilbert, S. J. (2005). The gateway hypothesis of rostral prefrontal cortex (area 10) function. In J. Duncan, L. Philllips, & P. McLeod (Eds.), *Measuring the mind: Speed, control and age* (pp. 217–248). Oxford: Oxford University Press.

Christoff, K., & Gabrielli, J. D. E. (2000). The frontopolar cortex and human cognition: Evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. *Psychobiology, 28,* 168–186.

Cockburn, J. (1995). Task interruption in prospective memory: A frontal lobe function. *Cortex, 31,* 87–97.

Crawford, J. R., & Garthwaite, P. H. (2002). Investigation of the single case in neuropsychology: Confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia, 40,* 1196–1208.

Crawford, J. R., Henry, J. D., Ward, A. L., & Blake, J. (2006). The Prospective and Retrospective Memory Questionnaire (PRMQ): Latent structure, normative data and discrepancy analysis for proxy-ratings. *British Journal of Clinical Psychology, 45,* 83–104.

Crawford, J. R., Howell, D. C., & Garthwaite, P. H. (1998). Payne and Jones revisited: Estimating the abnormality of test score differences using a modified paired samples *t* test. *Journal of Clinical and Experimental Neuropsychology, 20,* 898–905.

Damasio, H., & Damasio, A. R. (1989). *Lesion analysis in neuropsychology*. New York: Oxford University Press.

Einstein, G. O., & McDaniel, M. A. (2005). Prospective memory: Multiple retrieval processes. *Current Directions in Psychological Science, 14,* 286–290.

Fletcher, P. C., & Henson, R. N. (2001). Frontal lobes and human memory: Insights from functional neuroimaging. *Brain, 124,* 849–881.

Gilboa, A. (2004). Autobiographical and episodic memory—one and the same? Evidence from prefrontal activation in neuroimaging studies. *Neuropsychologia, 42,* 1336–1349.

Gilboa, A., Alain, C., He, Y., Stuss, D. T., & Moscovitch, M. (2009). Ventromedial prefrontal cortex lesions produce early functional alterations during remote memory retrieval. *Journal of Neuroscience, 29,* 4883–4893.

Gilboa, A., Alain, C., Stuss, D. T., Melo, B., Miller, S., & Moscovitch, M. (2006). Mechanisms of spontaneous confabulations: A strategic retrieval account. *Brain, 129,* 1399–1414.

Goschke, T., & Kuhl, J. (1993). Representation of intentions: Persisting activation in memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 19,* 1211–1226.

Grafman, J. (1995). Similarities and distinctions among current models of prefrontal cortical functions. *Annals of the New York Academy of Sciences, 769,* 337–368.

Harris, J. E. (1984). Remembering to do things: A forgotten topic. In J. E. Harris & P. E. Morris (Eds.), *Everyday memory, actions, and absent mindedness* (pp. 71–92). London: Academic Press.

Kardiasmenos, K. S., Clawson, D. M., Wilken, J. A., & Walllin, M. T. (2008). Prospective memory and efficacy of memory strategy in multiple sclerosis. *Neuropsychology, 22,* 746–754.

Lustig, C., & Hasher, L. (2001). Implicit memory is not immune to interference. *Psychological Bulletin, 127,* 618–628.

Marsh, R. L., Hicks, J. L., & Bink, M. L. (1998). Activation of completed, uncompleted and partially completed intentions. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 24,* 350–361.

McDaniel, M. A., & Einstein, G. O. (2000). Strategic and automatic processes in prospective memory retrieval: A multiprocess framework. *Applied Cognitive Psychology, 14,* S127–S144.

Moscovitch, M. (1994). Memory and working with memory: Evaluation of a component process model and comparisons with other models. In D. L. Schacter & E. Tulving (Eds.), *Memory systems* (pp. 269–310). Cambridge, MA: MIT Press.

Petrides, M. (1996). Specialized systems for the processing of mnemonic information within the primate frontal cortex. *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences, 351,* 1455–1461.

Petrides, M., & Pandya, D. N. (1994). Comparative architectonic analysis of the human and the macaque frontal cortex. In: F. Boller and I. Grafman (Eds.), *Handbook of Neuropsychology* Vol 4 (pp. 17–58). Amsterdam: Elsevier.

Schnider, A., Valenza, N., Morand, S., & Michel, C. M. (2002). Early cortical distinction between memories that pertain to ongoing reality and memories that don't. *Cerebral Cortex, 12,* 54–61.

Smith, E. E., & Jonides, J. (1999). Storage and executive processes in the frontal lobes. *Science, 283,* 1657–1661.

Smith, R. E. (2003). The cost of remembering to remember in event based prospective memory: Investigating the capacity demands of delayed intention performance. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 29,* 347–361.

Stuss, D. T., Alexander, M. P., Floden, D., Binns, M. A., Levine, B., McIntosh, A. R., et al. (2002). Fractionation and localization of distinct frontal lobe processes: Evidence from focal lesions in humans. In D. T. Stuss & R. T. Knight (Eds.), *Principles of frontal lobe functions* (pp. 392–407). New York: Oxford University Press.

Stuss, D. T., Alexander, M. P., Shallice, T., Picton, T. W., Binns, M. A., Macdonald, R., et al. (2005). Multiple frontal systems controlling response speed. *Neuropsychologia, 43,* 396–417.

Troyer, A. K., & Murphy, K. J. (2007). Memory for intentions in amnestic mild cognitive impairment: Time and event-based prospective memory. *Journal of the International Neuropsychological Society, 13,* 365–369.

Umeda, S., Nagumo, Y., & Kato, M. (2006). Dissociative contributions of medial temporal and frontal regions to prospective remembering. *Reviews in the Neurosciences, 17,* 267–278.

West, R., McNerney, M. W., & Krauss, I. (2007). Impaired strategic monitoring as the locus of a focal prospective memory deficit. *Neurocase, 13,* 115–126.

Worthington, A. (1999). Dysexecutive paramnesia: Strategic retrieval deficits in retrospective and prospective remembering. *Neurocase, 5,* 47–57.