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On the Role of Rostral Prefrontal Cortex (Area 10) in Prospective Memory

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This book is testament to the wonderful advances that have been achieved in the last few years in the field of prospective memory (PM[1]) research. However this is still a very new area of study. Also relatively new are the methods in cognitive neuroscience that enable us to localize the neural underpinnings of specific behavioral functions. So one might expect, at this early scientific stage, that the evidence that links particular brain regions to PM might be somewhat contradictory. Very surprisingly, however, this is not the case, at least for the frontal lobes. There is a general consensus that the executive functions of the frontal lobes play some part in supporting PM. This comes both from evidence of structural abnormality in the frontal lobes in people with an acquired PM deficit (e.g., Fortin, Godbout, & Braum, 2003) or through studies linking executive processing with PM performance (e.g., Kliegel, Eschen, & Thone-Otto, 2004; Knight, Titov, & Crawford, 2006; Mantyla, 2003; Marsh & Hicks, 1998; McDaniel, Glisy, Rubin, Guynn, & Routhieaux, 1999; Salthouse, Berish, & Siedlecki, 2004; but see Matthias & Mansfield, 2005).

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Most recently, there is early evidence that suggests a special role for one subregion of the frontal lobes: area 10. This region is also rather confusingly referred to in the literature as Brodmann's area 10; rostral prefrontal cortex; anterior prefrontal cortex; frontopolar cortex; or the frontal pole. This is a very interesting brain region. It is very large in humans: in volumetric terms probably the largest single architectonic region of the frontal lobes (Christoff et al., 2001), covering approximately 25 to 30 cubic centimeters (Semendeferi, Armstrong, Schleicher, Zilles, & Van Hoesen, 2001; see Figure 11.1). It is also in relative terms much larger in the human brain than in other animals, including the great apes (Semendeferi et al., 2001; but see Holloway, 2002). Additionally, this region is probably the last to achieve myelination, and it has been argued that tardily myelinating areas engage in complex functions highly related to the organism's experience (Fuster, 1997). These are all good reasons to imagine that the rostral prefrontal cortex may support cognitive processing, which is especially important to humans. Very recent evidence seems to suggest that this brain region may play a critical part in the supporting the processes that enable PM, which is perhaps one of the behavioral functions that most distinguishes humans from other animals (see, e.g., Einstein et al., 2005). This chapter is a review of the currently available evidence, which comes from two main sources. The first is lesion evidence; the second is evidence from functional brain imaging.

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[1] Delegates at the Second International Conference on Prospective Memory held in Zurich, Switzerland, in July 2005 voted to use the abbreviation PM in the future to refer to prospective memory. It should be noted, however, that this vote was not carried with an overwhelming majority, and elegant and principled arguments were presented in favor of other abbreviations, especially by Peter Graf.

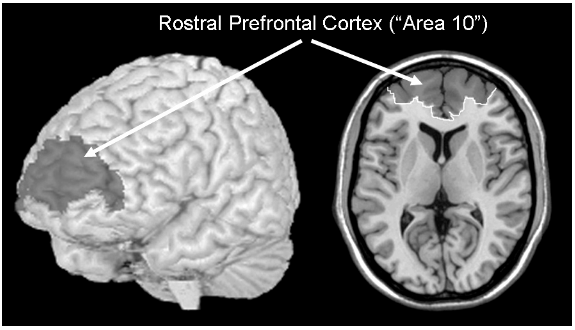

FIGURE 11.1 Approximate location of rostral prefrontal cortex, or Area 10 of the human brain (shaded in dark gray). It is the most anterior part of the brain, located just behind the forehead. The panel on the left shows the whole brain, with the front of the brain facing forward. The panel on the right is a transverse slice through the brain that shows the approximate depth of rostral prefrontal cortex. A simple way of understanding the orientation of this transverse slice is to imagine that the top of someone's head has been cut off, and the picture is what you would see if you were looking down into the skull.

AREA 10 AND PROSPECTIVE MEMORY: HUMAN LESION EVIDENCE

Perhaps the easiest way of making a link between the functions of particular brain regions and prospective memory would be to find a series of people with circumscribed cerebral involvement who have either isolated PM impairments (i.e., show no impairment on any other kind of test), or show isolated impairments at different stages of remembering to carry out a delayed intention. However to our knowledge this has not yet occurred. Of course, this could be because the appropriate patient has not yet been discovered. However, it is also possible that this is consistent with a view of prospective memory as a function rather than a construct, where *a function* is an observable set of behaviors evinced in pursuit of a particular contextually defined purpose, and *constructs* are hypothetical processing resources used in support of many functions (e.g., memory, attention, etc.; see Burgess et al., 2006, for definitions of functions and constructs). On this account, many theoretically independent processing resources (e.g., sustained attention, retrospective memory, inhibition, etc.) work together to enable the behavior called prospective memory. Consistent with this account is the view that these resources are used to enable other forms of behavior as well. If this is correct, then a processing impairment that produces a PM deficit will also be likely to cause observable deficits in other functions. Indeed, it is central to the notion of central processes in the field of executive functions that executive control processes contribute to a

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range of different behaviors, and low process–behavior correspondence is therefore concomitant (see Burgess, 1997, for further details).

Prima facie, this complicates investigations. However this situation, if true, actually means that examining the symptoms that coexist with the PM ones, and the situation in which they occur, can give a key insight into the processing components of PM. Indeed, in this way, to study only performance on PM tests would be a mistake. Instead, one ideally needs to understand the totality of the clinical picture of which a PM deficit is one component. This is most likely to give the concordant evidence that is required to characterize the central process. We illustrate this point next by demonstrating that prospective failures in everyday life, even where they occur in the context of unimpaired intellect, retrospective memory, or problem-solving skills, usually do so in the context of a specific problem with behavioral organization of which PM problems are one symptom.

PROSPECTIVE MEMORY FAILURES AS ONE SYMPTOM OF A WIDER SYNDROME

What would the everyday behavior of a person with a severe acquired PM deficit look like? If every intended action that could not be enacted immediately was not carried out, or was executed out of sequence, or in response only to environmental prompts, then the result would be widespread behavioral disorganization, not just failure on PM tests.

Perhaps the first description of such a person was reported 70 years ago. Penfield and Evans (1935) described the symptoms that Penfield's sister was experiencing after the removal of a right frontal glioma:

> She had planned to get a simple supper for one guest and four members of her family. She looked forward to it with pleasure and had the whole day for preparation. When the appointed hour arrived she was in the kitchen, the food was all there, one or two things were on the stove, but the salad was not ready, the meat had not been started and she was distressed and confused by her long continued effort alone.

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This impairment in carrying out daily activities would not have been remarkable were it the case that the patient was suffering from serious disabilities in basic cognitive systems (e.g., classic dense amnesia, visuospatial/perceptual or agnosic problems, disorders of motor control, etc.). However this was not the case with Penfield and Evans's patient, nor with others who were soon reported (e.g., Ackerly & Benton, 1947; Brickner, 1936). These established, at least on the grounds of clinical observation alone, that this kind of behavioral disorganization can be seen in the absence of these kinds of impairments.

However it was not until 50 years after Penfield and Evans's paper that an attempt was made to isolate the critical cognitive deficit underpinning this disorder. Eslinger and Damasio (1985) described the case of EVR, who had undergone surgical removal of a large bilateral frontal meningioma. At the time of his operation EVR was a financial officer with a small company and a respected member of his community. He was married and the father of two children; his brothers and sisters considered him a role model and a natural leader. After the operation however, EVR lost his job, went bankrupt, was divorced by his wife, and moved in with his parents. He subsequently married a prostitute and was divorced again within 2 years. Extensive psychological evaluations found no deficit; in fact, he was superior or above average on most tests (e.g., Verbal IQ of 125; Performance IQ of 124; no difficulty on Wisconsin Card Sorting Test [WCST]). He was also able to discuss intelligently matters such as the economy, foreign affairs, financial matters, or moral dilemmas. Despite these normal findings, EVR was often unable to make simple everyday decisions, such as which toothpaste to buy, what restaurant to go to, or what to wear. He would instead make endless comparisons and contrasts, often being completely unable to come to a decision at all. Further, Eslinger and Damasio (1985) reported PM problems: "It was as if he forgot to remember short- and intermediate-term goals" (p. 1737).

Eslinger and Damasio's (1985) paper was particularly important because it was the first convincing demonstration that this level of behavioral disorganization could occur in the context of intact intellect, and intact performance on some tests traditionally thought to be sensitive to deficits in "frontal lobe" executive functions. However it was not possible to determine from this case alone whether the emotional and psychosocial problems that EVR displayed were necessarily linked to his prospective memory problems, or whether they were just associated deficits resulting from a large frontal lesion. Scientific progress on this front was limited at that time by two interlinked shortcomings: (a) No qualitative assessment had yet been undertaken of these kind of patients' everyday life problems, and (b) no laboratory task had been developed that a priori reflected these difficulties. Without a qualitative assessment, one could not begin to determine the range of behaviors under examination, or the characteristics of the situations that presented problems for the patients, and without a representative laboratory task there was no simple "model of the world" that could form the basis for scientific investigation of the disorder at an information processing level.

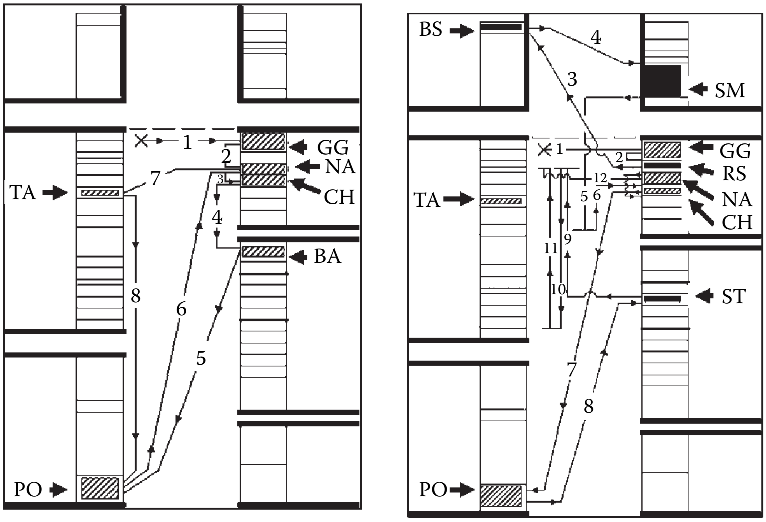
DISORGANIZATION IN EVERYDAY LIFE: FROM OBSERVATION TO EXPERIMENTATION

Shallice and Burgess (1991), however, addressed these issues. They presented three patients who had all suffered frontal lobe damage following traumatic brain injury. All three had no significant impairment on formal tests of perception, language, and intelligence and two performed well on a variety of traditional tests of executive function. Indeed, one of these cases (AP) was probably the best example of the syndrome so far reported (this case was later called NM by Metzler & Parkin, 2000). AP had sustained an open head injury in a road-traffic accident when he was in his early 20s. The injury caused a virtually complete removal of the rostral prefrontal cortex bilaterally plus damage to surrounding regions. On standard neuropsychological measures of intellectual functioning, memory, perception, and even traditional tests of executive function, AP performed within the superior range.

This is not to say that AP was unimpaired in other regards, however (Metzler & Parkin, 2000; Shallice & Burgess, 1991). The most noticeable of these in everyday life was a marked multitasking and PM problem. This manifested itself as tardiness and disorganization, the severity of which ensured that despite his excellent intellect and social skills, he never managed to make a return to work at the level he had enjoyed premorbidly. Shallice and Burgess (1991) invented two new tests of multitasking to assess these problems. The first of these tests, called the Multiple Errands Test (MET), was a real-life multitasking test carried out in a shopping center. Participants have to complete a number of tasks, principally involving shopping in an unfamiliar shopping center, while following a set of rules (e.g., no shop should be entered other than to buy something). The tasks vary in terms of complexity (e.g., buy a small loaf of bread vs. discover the exchange rate of the Euro yesterday), and there are a number of "hidden" problems in the tasks that have to be appreciated and the possible course of action evaluated (e.g., one item asks that participants write and send a postcard, yet they are given no pen, and although they cannot use anything not bought on the street to help them, they are also told they need to spend as little money as possible). In this way, the task is quite open-ended or ill-structured (i.e., there are many possible courses of action, and it is up to the individuals to determine for themselves which one they will choose).

The second task that Shallice and Burgess (1991) invented was a more controlled experimental task (the Six-Element Test [SET]). This required participants to swap efficiently among three simple subtasks, each divided into two sections within 15 minutes, while following some arbitrary rules (e.g., You cannot do Part A of a subtask followed immediately by Part B of the same subtask). There are no cues as to when to switch tasks, and although a clock is present, it is covered, so that checking it has to be a deliberate action. Thus this paradigm has a strong component of voluntary time-based task switching, one form of PM.

Despite their excellent general cognitive skills, AP and the other cases reported by Shallice and Burgess (1991) all performed these tasks below the 5% level compared with age- and IQ-matched controls. On the MET, the participants made a range of types of error, many of which could be interpreted as PM failures. For instance they would find themselves having to go into the same shop more than once to buy items that could all have been bought at one visit; not completing tasks that they had previously learned that they needed to do; not remembering to come over to the experimenter and tell them what they had bought when leaving a shop (a prelearned task rule); or going outside the boundaries of the shopping center (at the start of the test participants are shown the boundaries and told not to cross them; see Figure 11.2). They also made a range of social behavior errors (e.g., leaving a shop without paying, offering sexual favors in lieu of payment). Shallice and Burgess rather inelegantly termed this kind of behavioral disorganization in the context of preserved intellect and other cognitive functions the strategy application disorder.



Matched control

Person with rostral PFC lesion

FIGURE 11.2 Performance of a patient with rostral prefrontal cortex damage on the Multiple Errands Test (Shallice & Burgess, 1991), and a typical control matched for age, sex, and estimated premorbid ability (NART). The patient took twice as long as the control yet failed to complete a number of tasks (the control completed them all). He also went out of bounds (boundary indicated by hatched line at end of street); entered shops more times than was needed; entered shops that were not necessary for the task, and made a number of task and social rule breaks. The patient was, however, able to repeat the task rules correctly both before and after the test.

It was not possible on the basis of Shallice and Burgess's (1991) data, however, to speculate on the anatomical localization of the lesion critical for this pattern of deficit, as the patients had suffered large traumatic lesions. Two years later however, Goldstein, Bernard, Fenwick, Burgess, and McNeil (1993) described a case that began to suggest a possible locus. This 51-year-old right-handed man (GN) had undergone a left frontal lobectomy 2.5 years earlier following the discovery of a frontal lobe tumor (mixed astrocytoma-oligodendroglioma). A 5-cm resection of left frontal lobe from the frontal pole was undertaken. From the point of view of traditional neuropsychological tests, this surgery made little difference to his cognitive abilities (e.g., Verbal IQ of 129, Performance IQ of 111; Story Recall Immediate 75–90th percentile, Delayed 50–70th percentile; Rey–Osterreith Delayed Figure Recall 80–90th percentile; Trail-Making 70–75th percentile). However, this did not reflect the change in his everyday competence. The patient had held a senior management position within an international company, but 2 years after surgery he had to take medical retirement because of increasing lethargy. He worked from home as a freelance management consultant, but had difficulty making decisions, culminating in his taking 2 weeks to decide which slides to use for a work presentation, but never actually reaching a decision. He also experienced anger control difficulties.

Goldstein et al. (1993) administered Shallice and Burgess's (1991) MET. GN made significantly more errors than controls, being less efficient (e.g., having to return to a shop), breaking task rules (e.g., using a stamp that another customer gave him), misinterpreting tasks (e.g., sticking the stamp on the wrong card), and failing to complete some tasks altogether, reporting that he had known he had to do them but somehow "forgot" them. He also showed some social rule breaks. For instance, he had forgotten to find out the price of tomatoes while in the grocery store earlier, and realizing that he should not go back into the shop unless he was to buy something, he very conspicuously climbed onto the fruit display outside the shop and peered in the shop window.

This case, and others reported in the literature, show a remarkably similar pattern of neuropsychological test performance. Burgess (2000b) summarized the performance of eight well-known cases: None of the cases had any language or visuoperceptual impairment and all scored within the superior range on tests of current intellectual functions. Four of the seven showed no impairment on any memory test. Most remarkably, two showed no impairment on a range of clinical executive function tests known to be sensitive to frontal lobe lesions. Moreover, no executive test has been failed by more than two of the eight cases. Most remarkably, two tasks have been administered to all the patients—the WCST and Verbal Fluency—and have been performed well by every case. This contrasts with the observation that all of the reported cases of strategy application disorder who have been given either the MET or SET have failed at least one of them.

THE RELATION BETWEEN PROSPECTIVE MEMORY AND LONG-TERM MULTITASKING

The kind of multitasking just described critically requires PM. Multitasking is a behavioral-level description that has a precise meaning in cognitive neuroscience. Burgess (2000a, 2000b) describes eight features of a situation that requires multitasking, the first five of which are axiomatic, plus a further three that are usually true of everyday-life multitasking situations:

Many tasks. A number of discrete and different tasks have to be completed.

Interleaving required. Performance on these tasks needs to be dovetailed to be time-effective.

One task at a time. Due to either cognitive or physical constraints, only one task can be performed at any one time.

Delayed intentions. The times for returns to task are not signaled directly by the situation.

No immediate feedback. There is no moment-by-moment performance feedback of the sort that participants in many laboratory experiments will receive. Typically, failures are not signaled when they occur.

Interruptions and unexpected outcomes. Unforeseen interruptions, sometimes of high priority, will occasionally occur, and things will not always go as planned.

Differing task characteristics. Tasks usually differ in terms of priority, difficulty, and the length of time they will occupy.

Self-determined targets. People decide for themselves what constitutes adequate performance.

In this way, multitasking may be different, at least in some regards, in the information processing demands it makes from multiple-task performance, which is where someone is performing several tasks simultaneously (or dual-tasking where there are two tasks; e.g., Baddeley, Della Salla, Gray, Papagno, & Spinnler, 1997). Prototypical dual- or multiple-task situations are air traffic control, or operating a computer while talking to someone on a telephone. There is little obvious PM demand in dual-task situations because the retention interval over which an intention is to be maintained is typically so short. By contrast, many real-life multitasking situations involve the coordination and dovetailing of many activities over longer time scales (e.g., Alderman, Burgess, Knight, & Henman, 2003). These typically require one to perform one particular task at a time (e.g., writing a scientific paper) while bearing in mind that other unrelated tasks have to be performed before completion of this task (e.g., collect the car from the workshop at 1 p.m.) and often having to periodically check the state of something else (e.g., has the expected e-mail arrived yet?). In other words, multitasking and multiple-task situations share Characteristics 1 and 2 above (plus in some situations 5), but only multitasking has Characteristics 3 and 4. These characteristics necessitate the involvement of PM (e.g., Kvavilashvili & Ellis, 1996) or the carrying out of an intended action—in this case a task switch—after a delay. Indeed, we would argue that the most common example of a PM action in everyday life is in the dovetailing of one's daily activities. Without this ability, one's behavior would be very inefficient. For instance, one would have to always finish one task (e.g., cooking the vegetables for a meal) before starting another (e.g., cooking other parts of the main meal), and operations that involve the integration of many subgoals (e.g., visiting a number of different shops during one shopping trip) would be performed highly inefficiently.

WHAT ARE THE CRITICAL BRAIN REGIONS THAT SUPPORT THE PROSPECTIVE MEMORY COMPONENT OF MULTITASKING?

There is now some evidence that this PM component of multitasking can be localized. The largest human group lesion study to date in this area was published by Burgess, Veitch, Costello, and Shallice (2000), who examined a series of 60 acute neurological patients (approximately three quarters of whom were suffering from brain tumors) and 60 age- and IQ-matched healthy controls on a multitasking test called the Greenwich Test. In this test, participants are presented with three different simple tasks and told that they have to attempt at least some of each of the tasks in 10 minutes, while following a set of rules. One of these rules relates to all subtests ("In all three tasks, completing a red item will gain you more points than completing an item of any other color") and there are four task-specific rules (e.g., "In the tangled lines test you must not mark the paper other than to write your answers down"). Thus this is a multitasking test where the majority of the variance in performance of the test comes from rule infractions rather than task-switching problems. The Greenwich Test was administered in a form that allowed consideration of the relative contributions of task rule learning and remembering, planning, plan following, and remembering one's actions to overall multitasking performance. Specifically, before participants began the test, their ability to learn the task rules (by both spontaneous and cued recall) was measured; this measure was called learn. They were then asked how they intended to do the test, and a measure of the complexity and appropriateness of their plans was gained (a variable called plan). This enabled us to look at whether their failures could be due to poor planning (see Kliegel, McDaniel, & Einstein, 2000; Kliegel, Phillips, Lwemke, & Kopp, 2005, for a similar approach). The participants then performed the task itself and by comparing what they did with what they had planned to do, a measure of plan following was made. Multitasking performance (the number of task switches minus the number of rule breaks) was referred to as the test score. After these stages were finished, participants were asked to recollect their own actions by describing in detail what they had done (variable name: recount). Finally, delayed memory for the task rules was examined (remember).

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A basic finding was that this sort of procedure is sensitive to a range of cognitive problems: Despite no differences between the controls and patients on measures of premorbid (NART) or current fluid intelligence (Raven's Advanced Progressive Matrices), the patients showed significant impairment on most of the variables (a similar finding is reported by Levine et al., 2000). At a more specific level however, lesions in different brain regions were associated with impairment at different stages in the multitasking procedure. Lesions to a large region of superior posterior medial cortex including the left posterior cingulate and forceps major gave deficits on all measures except planning. Remembering task contingencies after a delay was also affected by lesions in the region of the anterior cingulate. Critically, however, Burgess et al. (2000) found that patients with left hemisphere rostral prefrontal cortex lesions, when compared with patients with lesions elsewhere, showed a significant multitasking impairment (i.e., the variable score) despite no significant impairment on remembering task rules (remember variable). Indeed, the left rostral prefrontal cases showed no significant impairment on any variable except the one reflecting multitasking performance. In other words, despite being able to learn the task rules, form a plan, remember their actions, and say what they should have done, they nevertheless did not do what they said that they intended to do. This can make a striking impression when one is administering the test: The participant says, for example, that he or she will attempt Tasks X, Y, and Z in that order, and may even say how long he or she intends to spend on each, plus describes how he or she will follow the task rules (e.g., "I will replace the lid on the bead box every time I take a bead out of the bead box."). However after starting the test just a minute or so later, the participant will actually not carry out any of these intended acts.

This link between rostral prefrontal cortex damage and this PM component of multitasking accorded well with the lesion location of Goldstein et al.'s (1993) previous single case. Moreover, two of the original three patients reported by Shallice and Burgess (1991) also had lesions affecting the rostral parts of the left frontal lobe. However a specific problem is presented by other findings. Thus one of Shallice and Burgess's (1991) cases had principally a right frontal lesion. Moreover Levine and colleagues (e.g., Levine, Freedman, Dawson, Black, & Stuss, 1999; Levine et al., 2000; Levine et al., 1998) have repeatedly implicated right hemisphere lesions in poor performance on their multitasking test, the R-SAT. As Levine et al. (2000) pointed out, these apparently conflicting results may be a result of the use of multitasking tests with differing characteristics: The Burgess et al. (2000) study applied a test where the variable taken as an estimate of multitasking ability was based principally on rule following rather than task switching. However, Levine et al.'s task (R-SAT) is more similar to Shallice and Burgess's (1991) original SET, in that the emphasis is on voluntary time-based task switching rather than rule following. So the lesion location differences could occur if task switching and rule following are not equivalent in information processing terms. This is certainly plausible with reference to the known characteristics of event- or time-based PM (see, e.g., Kvavilashvili & Ellis, 1996). Moreover, a recent group study of real-world multitasking in mixed etiology neurological patients (Alderman et al., 2003) demonstrated a double dissociation between rule following and failures to initiate tasks. An alternative possibility, however, is that the difference between the findings of Levine's group and Burgess's group may instead be due to the differing populations studied by them: Levine's finding are based principally on traumatic brain injury, but the Burgess et al. (2000) study used acute circumscribed lesions (principally tumors).

A resolution to this apparent paradox was provided by a recent human group lesion study by Burgess, Veitch, and Costello (reported in Burgess et al., 2006). In this study, a new version of the Burgess et al. (1996) SET of multitasking was given to 69 acute neurological patients with circumscribed focal lesions and 60 healthy adults, using the administration framework of Burgess et al. (2000). The SET differs from the Greenwich Test in that the multitasking score reflects mainly voluntary time-based switching rather than rule following. Compared with other patients, those whose lesions involved the rostral prefrontal regions of the right hemisphere made significantly fewer voluntary task switches, attempted fewer subtasks, and spent far longer on individual subtasks. They did not, however, make a larger number of rule breaks (in contrast to the left rostral patients in the Burgess et al., 2000, study). As with the study of Burgess et al. (2000), these multitasking deficits could not be attributed to deficits in general intellectual functioning, rule knowledge, planning, or retrospective memory.

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Considering now the previous single case studies in the context of these group study findings, it is clear that there is a remarkably consistent finding of involvement of Area 10 in patients who have high-level disorganization in everyday life. For instance, in the six cases reviewed by Burgess (2000b) for whom good brain scan data were available, all of them had rostral prefrontal cortex involvement of either the left or right hemispheres (or both). In addition to these cases, we might now also add the recent case of Bird, Castelli, Malik, Frith, and Husain (2004) who had suffered a rare form of stroke affecting the medial aspects of Area 10 bilaterally, and who failed the SET, despite passing some other executive tests (e.g., the WCST). It seems likely that PM problems (and therefore multitasking ones) are just one indicator of the problems these unfortunate people experience.

SUMMARY OF EVIDENCE FROM HUMAN LESION STUDIES

Although it is a widespread belief that human lesion studies show that PM must be supported in part by the frontal lobes (e.g. Cockburn, 1995) there is actually surprisingly little direct evidence (see, e.g., Daum & Mayes, 2000). However, what little evidence there is broadly supports this view. We have argued here that some of the critical components supported by the frontal lobes that contribute to PM also contribute to other behaviors. In this way we expect that patients with even relatively isolated PM deficits will show concomitant deficits (i.e., will fail tests other than PM ones, if the appropriate procedure is given). However there is now enough evidence to suggest that these concomitant deficits need not be in the domains of language, simple memory (e.g. recognition), perception, or even those abilities indexed by performance on many traditional executive function tests (e.g., Tower of London, WCST). There is enough evidence to suggest that, more specifically, rostral prefrontal cortex plays a critical part in the ability to carry out what you intended to do after a delay, beyond what can be explained by planning or retrospective memory. So what is the nature of this processing impairment that can leave so many domains of cognition intact, but cause PM failures and also other symptoms (e.g., social behavior abnormalities)?

THE ROLE OF ROSTRAL PREFRONTAL CORTEX IN PROSPECTIVE MEMORY: NEUROIMAGING EVIDENCE

Working on the basis that deficits in PM were the core impairment in rostral patients with multitasking deficits, Burgess, Quayle, and Frith (2001) tested the link between rostral prefrontal cortex and PM using positron emission tomography (PET). Regional cerebral blood flow (rCBF) increases in lateral Brodmann's area (BA) 10 were indeed found in PM conditions relative to the ongoing task alone. This finding was in agreement with that of Okuda et al. (1998), who also found increases in the left frontal pole. However Okuda et al. were unable to determine whether this activation was associated with intention maintenance, target detection, or the requirement for "dividing attention between the planned action and the routine activity" (p. 127). The Burgess et al. (2001) study helped in this respect, by including a condition where participants were told that an intention cue or target might appear, but none actually did. Critically, rCBF increases in lateral BA 10 were also discovered in this condition, where there is only the expectation of an intention cue, and a cue is never witnessed or responded to. Thus lateral BA 10 is more involved with the maintenance of an intention rather than cue recognition or intention execution.

A second PET study confirmed the role of lateral BA 10 in PM conditions, but also showed that medial BA 10 is more active in ongoing conditions than PM ones (Burgess, Scott, & Frith, 2003). Furthermore, medial BA 10 was also more active (compared with PM conditions) in a simple attentional baseline condition where the participant just responded as fast as possible to any change on the display.

The two Burgess et al. PET studies had used a conjunction experimental design in which one investigates hemodynamic changes common to tasks that putatively stress the process of interest (Shallice, 1988) but where the other demands of the tasks are made quite different, by, for example, using spatial material for one, and verbal for the other. Accordingly, Burgess et al. (2003) interpreted their results as suggesting that the functions supported by BA 10 in PM are "central" in the respect that they are material nonspecific, and unrelated to precise intention retrieval or cue recognition demands. Instead, Burgess et al. favored an explanation in terms of one of the possibilities raised by Okuda et al. (1998), that the rostral prefrontal cortex rCBF changes were related to the attentional demands made by having to "bear in mind" an intention while performing an ongoing task.

Simons, Schölvinck, Gilbert, Frith, and Burgess (2006) explicitly tested this hypothesis by measuring brain activity (using function MRI [fMRI], and a conjunction of two different PM tasks: words and shapes) while manipulating the demands on either recognizing the appropriate context to act (cue identification) or remembering the action to be performed (intention retrieval). In the word task, each trial consisted of two nouns presented next to each other in the middle of the screen, one of which was written in uppercase and the other in lowercase letters. For ongoing trials, participants were instructed to indicate using a keypad whether the left or the right word contained more letters. However, if the words belonged to the same semantic category (e.g., *cow* and *horse*), a different key was to be pressed (cue identification PM condition). Furthermore, if the words were written in the same case, participants were required to count up the syllables of both words and indicate using the keypad whether the total was four or less, or higher than four (intention retrieval PM condition).

The stimuli in the shape task consisted of a 4 × 4 grid, in which a colored triangle and a random other shape, such as a pentagon, were presented. For ongoing trials, participants were instructed to indicate whether the shape that was not the triangle was presented to the left or the right of the triangle. However, if the two shapes were, spatially, a chess knight's move away from each other, participants were instructed to press a different key (cue identification PM condition). In addition, if the two shapes were of the same color, participants were required to determine the number of sides of the shape other than the triangle, and indicate whether this number was below or equal to five, or above five (intention retrieval PM condition).

A consistent pattern of hemodynamic changes was found in anterior prefrontal cortex (BA 10) across both types of task, and across both PM conditions (compared with the ongoing task): There was activation in lateral BA 10, which was

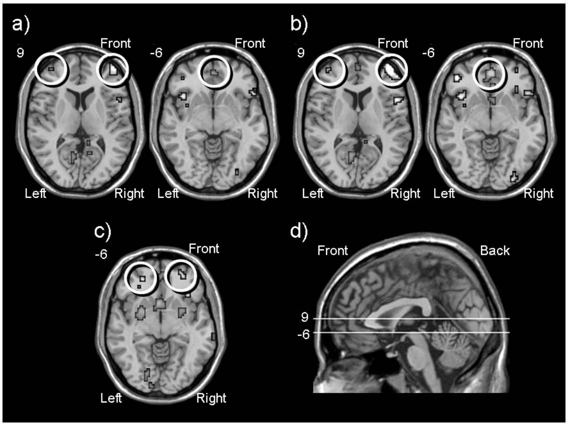

FIGURE 11.3 Data from Simons, Schölvinck, Gilbert, Frith, and Burgess (2006) indicating that cue identification and intention retrieval components of prospective memory have a largely common neural basis in anterior prefrontal cortex (BA 10). Activations of principal interest are circled. Z coordinates are shown in the top left corner of each axial image, and the inferior–superior location of the slices is indicated on the sagittal projection shown in (d). (a) Contrasting cue identification PM trials with ongoing trials, bilateral BA 10 activation (9 slice), and medial BA 10 deactivation (-6 slice) was observed. A highly similar pattern is shown in (b), the intention retrieval PM versus ongoing contrast. Differences between conditions emerge in (c), the direct intention retrieval PM > cue identification PM contrast, with significantly greater activation in anterior prefrontal cortex bilaterally in the intention retrieval PM condition, and evidence of deactivation in medial anterior BA 10.

accompanied by deactivation in medial BA 10. However, direct comparison of the high intention retrieval demand with the high cue recognition demand PM conditions also revealed greater activation in lateral BA regions bilaterally in the intention retrieval condition. These regions were located somewhat more medially than those that showed activation common to both conditions (see Figure 11.3). Simons et al. (2006) argued that the regions that were activated in both PM conditions may reflect the requirement in PM tasks for the biasing of attention between external events (e.g., identifying the cue amid distracting stimuli) and internal thought processes (i.e., maintaining the intention and remembering the intended actions). However it also seems from the comparison of the two PM conditions that there are some subregions of BA 10 that are more sensitive to particular PM task characteristics.

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Further evidence for the specificity of some regions of BA 10 comes from a recent paper by Okuda et al. (submitted). In two PET studies, brain activity associated with time-based versus event-based PM tasks was examined. In the time-based condition of the first study, young healthy volunteers were asked to make a response based on their self-estimation of the passage of time while engaged in an attention-demanding ongoing activity. In the time-based condition of the second study, participants had a clock available. Both studies showed activation differences in rostral prefrontal cortex (principally BA 10) according to whether the task was time- or event-based.

In Study 1, participants performed two prospective memory tasks (time, event) and a baseline task required the ongoing activity alone. The ongoing activity was a serial addition task. A digit, randomly selected from one to nine, was presented binaurally every 3 seconds and the participants were required to add up the digits one by one and report the sum immediately after the presentation of each digit. The prospective response was to clench both hands. In the time-based task, the participants were asked to make the prospective response once during the first 30 seconds, twice during the next 30 seconds, once during the third 30 seconds, and once during the last 30 seconds after the task started. In the event-based task, they were asked to make the prospective memory response when a cue stimulus (the number 7) was presented during the ongoing activity. The cue stimulus was presented once during the first 30 seconds, twice during the next 30 seconds, once during the third 30 seconds, and once during the last 30 seconds. Okuda et al. (submitted) found in this experiment that an area of left lateral superior rostral prefrontal cortex (BA 9/10; peak coordinates $x = -16$, $y = 48$, $z = 24$) was more active during the time-based PM condition than during either the event-based PM one or the ongoing task alone (see Figure 11.4).

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Okuda et al.'s (submitted) second experiment used a conjunction design, looking at the activations common to two different PM tasks: verbal or nonverbal, each presented in three conditions (time PM, event PM, ongoing task only). In the verbal tasks, the ongoing task required the participants, when presented with pairs of words, to make a same–different judgment based on the number of syllables in each word. For the ongoing task of the nonverbal conditions, participants were presented with a pair of rectangles and had to judge if the shapes were identical, regardless of their orientation. In the time PM conditions of each task, a clock was always presented at the center of the screen, which updated every 1 second to indicate current time from the start of the task. Participants were asked to press a button every 1 minute after starting the task, and were told that they could use the information of the clock to help them. In the event PM conditions, participants were asked to press a button whenever they encountered a cue stimulus, which was the word *guitar* in the verbal tasks, or exact squares in the nonverbal tasks.

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In contrast to the first study, a region of increased rCBF was found in left lateral rostral prefrontal cortex during the event-based PM conditions compared with the time-based conditions (Figure 11.4c). This region was somewhat inferior within BA 10 to that found in Experiment 1 (Figure 11.4a). Across both studies, rCBF in the rostro-medial prefrontal cortical regions increased during the time-based task and the ongoing-alone task as compared with the event-based task. These regions were more rostral, superior, and closer to the midline than the medial BA 10 regions identified in Experiment 1. (The aspect of exactly *where* within BA 10 the activations occurred will become important in the discussion of the functions of BA 10 later.) It is probably too early within our understanding both of the dynamics of PM tasks, and of the functional architecture of BA

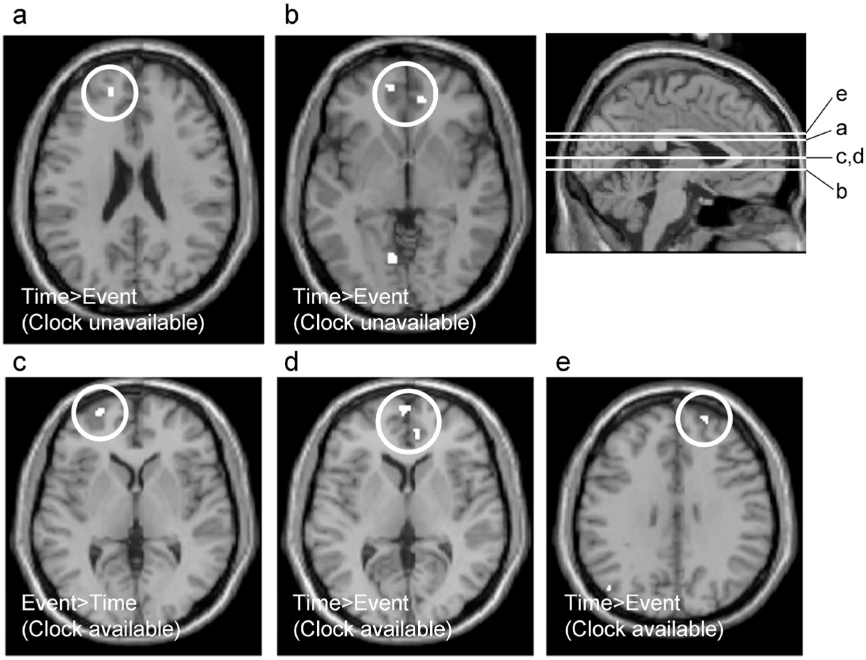

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FIGURE 11.4 Areas of activation during time- and event-based prospective memory tasks according to Okuda et al. (submitted). Activation foci, encircled with a white ring, were superimposed on horizontal sections of anatomical MRI of the standard brain. (a) and (b) show greater activation during time-based tasks than during event-based tasks, where participants had to estimate timing for time-based prospective response (Study 1). (c) shows greater activation during event-based tasks than during time-based tasks, where a clock was available for time-based prospective response (Study 2). (d) and (e) show greater activation during time-based tasks than during event-based tasks in Study 2. The top right panel shows the height level of each section (white lines) within the brain on a midsagittal section of the standard anatomical MRI.

10 to reach a full explanation of these results. However they do seem to suggest that brain activity in the rostral prefrontal cortex shows different patterns during the performance of time- and event-based PM tasks. Furthermore, they seem to suggest that subregions of BA 10 are differentially involved in time-based tasks according to whether or not a clock is present as an aid to the passage of time. One possibility to explain this latter phenomenon that relates to the explanation of the Simons et al. (2006) findings earlier, is that having a clock available increases the degree to which the participant attends to environmental stimuli rather than maintaining a continually updated, self-generated representation of the passage of time. In other words, it changes the relative amount of stimulus-oriented or stimulus-independent attending).

FROM PROSPECTIVE MEMORY TO THE "GATEWAY HYPOTHESIS" OF BA 10 FUNCTION

In a series of experiments in our lab, we have investigated this possibility that BA 10 is sensitive to differences in the degree to which cognition is stimulus-oriented or stimulus-independent. If BA 10 supports a mechanism that enables us to either maintain thoughts in our head (i.e., stimulus-independent cognition) while doing something else, or switch between the thoughts in our head and attending to events in the environment (stimulus-oriented attending) then one would indeed expect that BA 10 would play a central role in prospective memory. However it should not be the only ability that this region supports, because one can conceive of situations that require these psychological functions without having the characteristic of maintaining an intention over a delay period. So if we could design a paradigm that stresses this psychological mechanism but is not a PM task, and it activates BA 10 in a neuroimaging experiment, then this account is lent weight.

Accordingly, three functional neuroimaging experiments carried out in our laboratory investigated the evidence that BA 10 is sensitive to differences in the source of the representations that are currently active in one's mind (for overviews see Burgess, Gilbert, Okuda, & Simon, 2006; Burgess, Simons, Dumontheil, & Gilbert, 2005). On this account, some thoughts are stimulus independent, in the sense that they are self-generated (e.g., inventing a novel story) or are not prompted by things currently experienced or witnessed (e.g., mind wandering). However, some thoughts are directly provoked by, or oriented toward, stimuli that one can see (e.g., reading). In this way, the hypothesis was that BA 10 might act as an attentional gateway between inner mental life and the external world as experienced through the senses.

The first experiment to test this hypothesis was presented by Gilbert, Frith, and Burgess (2005). They contrasted, using fMRI, the neural activation that occurs when people are performing tasks using stimuli presented on a display with activation that occurs when they are performing the same tasks "in their heads." BA 10 was found to be activated in the condition where people are using externally displayed stimuli (i.e., stimulus-oriented attending or SO) compared with when they are doing the same task in the absence of relevant stimuli (stimulus-independent cognition or SI). It also showed lateral BA 10 activation at the points where participants switched between either condition, regardless of the direction of the switch (i.e., SO –> SI; SI –> SO). Thus the existence of a neural mechanism that arbitrates between stimulus-independent and stimulus-oriented thought received support, and a link between this mechanism and rostral prefrontal cortex seemed a promising line of enquiry. A further fMRI study (Gilbert, Simons, Frith, & Burgess, 2006) demonstrated performance-related activation (i.e., increased activation was associated with faster reaction times) in medial BA 10 in simple reaction time conditions that did not require substantial stimulus processing. Thus the characterization of medial rostral prefrontal cortex as most active when an unusual degree of attention to external stimuli is required was supported.

Burgess et al. then considered the possible role of lateral rostral prefrontal cortex. The findings of a patient's problems with multitasking, and previous functional imaging studies of prospective memory (e.g., Burgess et al., 2001; Burgess et al., 2003)

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suggest a role for this subregion of BA 10 in stimulus-independent cognition. However there are different forms of both stimulus-oriented and stimulus-independent attending. So Burgess, Dumontheil, Gilbert, and Frith (submitted) examined the main forms of both to determine whether the lateral–medial distinction holds for all forms, and whether there is evidence for further functional specialization within lateral or medial BA 10. Two quite different tasks were given under four conditions in a conjunction design. The conditions varied in the degree to which they made demands on five attentional constructs, two of which were stimulus-oriented (vigilance and stimulus attending) and three of which were stimulus-independent in nature (mind wandering; use of self-generated representations; and maintenance over a delay). Regardless of task, conditions stressing both of the stimulus-oriented attentional forms activated medial BA 10, and all three that stressed stimulus-independent cognition activated lateral BA 10 (see Figure 11.5). There was

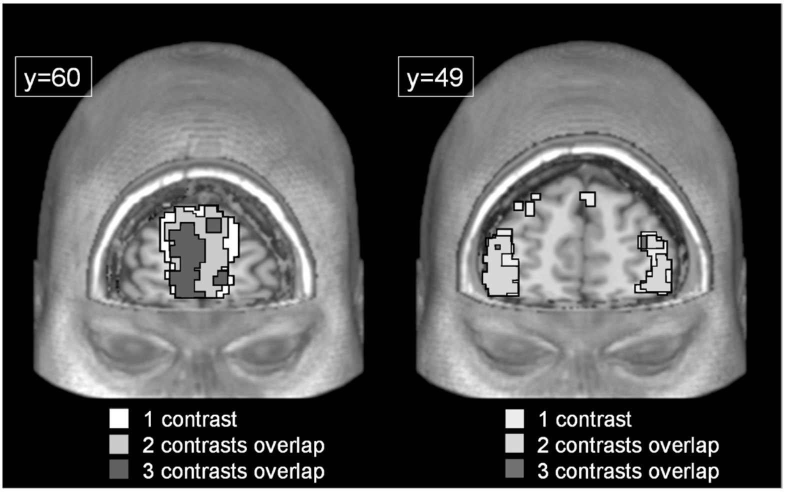

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FIGURE 11.5 Results from Burgess, Dumontheil, et al. (submitted). On the left is shown a coronal slice of the brain at y = 60. The shades of gray represent the areas of activation, and overlaps between the activations, during three conditions (Conditions 1, 2, and 4) that stressed stimulus-oriented cognition compared with a condition that made a high demand on stimulus-independent thought (Condition 3). So the darkest shaded regions, for instance, indicate that all three stimulus-oriented conditions activated this area: a large region of medial BA 10. On the right is a coronal slice of the brain at y = 49, demonstrating a second set of contrasts, and the overlaps between the areas revealed by them. The contrasts compare Conditions 1, 3, and 4, which had a substantial stimulus-independent component, to Condition 2, where attention is just maintained on stimulus-oriented thoughts. Lateral BA 10 regions are revealed by these contrasts, and there is substantial overlap in the location of the activations demonstrated by them.

limited evidence for further functional specialization. Thus the gateway hypothesis did indeed approximate BA 10 findings across a range of conditions and tasks.

FROM THE GATEWAY HYPOTHESIS BACK TO PROSPECTIVE MEMORY

These results indicate that there may be a general principle for the functional organization of at least some parts of human brain BA 10. This view receives further support from a meta-analysis conducted by Gilbert, Spengler, Simons, Frith, and Burgess (2006). They analyzed the reaction times to paradigms from 104 PET/fMRI studies, yielding 133 independent contrasts. The tasks that had provoked these activations came from a wide range of functions (e.g., memory, mentalizing, perception, and PM). A fascinating general principle emerged. Gilbert, Spengler, Simons, Frith, et al. (2006) found that reaction times to tasks that had provoked lateral BA 10 activations tended to be slower than reaction times in whatever control task had been used. The pattern occurred regardless of the type of task under study, and thus seems to be a general principle of BA 10 neuroimaging findings. If lateral BA 10 plays some part in affecting tasks that require the various forms of stimulus-independent cognition as argued here, this pattern would be expected. This is because reaction times to tasks that require attending to stimuli plus some form of stimulus-independent thought (e.g., performing an ongoing task while maintaining an intention, checking for PM cues, etc.) will be longer, typically, than to tasks that only require the stimulus-attending component (e.g., the ongoing task alone). This result also accounts for the consistent findings of rostral prefrontal cortex activation in paradigms where there may be expected to be a novel degree of juxtaposition between stimulus-oriented and stimulus-independent thought, either induced intentionally by the task or because of spontaneous task-irrelevant thoughts (e.g., PM and other multitask and switching paradigms; e.g., Braver & Bongiolatti, 2002; Burgess et al., 2001; Burgess et al., 2003; Dreher, Koechlin, Ali, & Grafman, 2002; Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999; Koechlin, Corrado, Pietrini, & Grafman, 2000; Okuda et al., 1998; Pollmann, 2001, 2004; or memory control processing, e.g., Fletcher & Henson, 2001; Herron, Henson, & Rugg, 2004; see Gilbert, Spengler, Simons, Steele, et al., 2006, for review).

However, although there may be general principles for the organization of BA 10 functions, this does not mean that there is not specialization within these parameters. Thus Gilbert, Spengler, Simons, Steele, et al. (2006) investigated, using the neuroimaging database described earlier, the location of activations within BA 10 according to the type of task being used. They found evidence for specialization of function within BA 10, with mentalizing tasks tending to provoke activations within caudal medial aspects of BA 10, episodic memory tasks (i.e., retrospective memory) being associated with lateral BA 10 activations, and paradigms that required the coordination of two or more activities (including prospective memory) being associated with very rostral activations within BA 10 (see Figure 11.6).

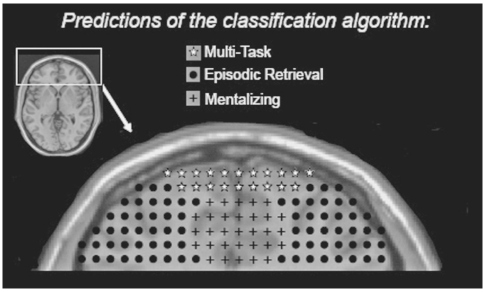

FIGURE 11.6 Results from the classification algorithm developed by Gilbert, Spengler, Simons, Steele, et al. (2006). This figure shows the predicted regions of activation for three types of task: those involving episodic retrieval (i.e., retrospective memory), mentalizing (e.g., theory of mind and other metacognitive judgments), and multitasking (any task involving the coordination of more than one task, including prospective memory paradigms). Results are plotted on an axial slice of a normalized T1 weighted image (z = 0).

CONCLUSION

There is a gathering consensus among PM researchers that the cognitive resources that underpin the episodic memory aspects of remembering a delayed intention are in some senses separable from those that support the control processing and attentional aspects of performance (e.g., Brandimonte & Passolunghi, 1994; Ellis, Kvavilashvili, & Milne, 1999; Groot, Wilson, Evans, & Watson, 2002; Marsh, Hicks, & Cook, 2005; Maylor, Smith, Della Sala, & Logie, 2002; McDaniel, Guynn, Einstein, & Breneiser, 2004; Park, Hertzog, Kidder, Morrell, & Mayborn, 1997; Sheeran, Webb, & Gollwitzer, 2005; Smith & Bayen, 2006; see also Burgess et al., chap. 11, this volume; Guynn, chap. 3, this volume; Kliegel, Jäger, Altgassen, & Shum, chap. 13, this volume; Marsh, Hicks, & Cook, chap. 4, this volume; Maylor, chap. 10, this volume; Smith, chap. 2, this volume). On most conceptions, episodic (or retrospective memory) resources are used principally in, for example, maintenance of the intention trace, recognizing the prospective cue, remembering what it was that had to be performed, and so forth. By contrast, the control, executive, or attentional resources are used to effect active rehearsal of the intention; monitoring and maintaining an increased state of preparedness; dividing attention or switching between the ongoing task and intention rumination; determining the allocation of attentional resources to either the ongoing task or to detecting the PM cue; and also strategic and motivational aspects of performance. Indeed, much recent research into the experimental psychology of PM is concentrating on the nature of these attentional resources and the demands made on them by PM tasks (e.g., Cohen, Dixon, Lindsay, & Masson, 2003; Einstein et al., 2005; Hicks, Cook, & Marsh, 2005; McGann, Ellis, & Milne, 2002; Nowinski & Dismukes, 2005; West, Krompinger, & Bowry, 2005; see also Guynn, chap. 3, this volume; Kliegel, Jäger, Altgassen, & Shum, chap. 13, this volume; Marsh, Hicks, & Cook, chap. 4, this volume; McDaniel, Einstein, & Rendell, chap. 7, this volume; Moscovitch, chap. 14, this volume; Phillips, Henry, & Martin, chap. 8, this volume; Smith, chap. 2, this volume). Moreover, it is in support of this resource that many researchers identify the role of frontal lobe structures (e.g. McDaniel et al., 1999).

However it seems that we can now be a little more precise perhaps than referring just to the frontal lobes in general. No doubt processes supported by many structures within the frontal lobes are utilized in the formulation and execution of delayed intentions. However one subregion of the frontal lobes that seems on present evidence to play a particularly significant role is brain BA 10, the most anterior aspects of the frontal lobes. Patients with damage to this region show various forms of failing to carry out delayed intentions, and neuroimaging studies of PM paradigms have consistently activated this region. However, patients with damage to this region need not show retrospective memory problems, and neuroimaging studies of episodic memory have tended to associate BA 10 with control or executive aspects of memory. Therefore it seems most plausible at present that the role that the processes that BA 10 supports in PM are bound up with the control or attentional components of PM functions.

As outlined earlier, one hypothesis that we have been pursuing is the role of BA 10 in PM and the requirement that PM tasks make on the active control of stimulus-independent versus stimulus-oriented (or driven) cognition, and especially in the requirement to switch between these attentional modes. This is because actively maintaining an intention while performing some other task necessarily requires stimulus-independent thought (i.e., because you are thinking about something other than what you are currently witnessing), and also stimulus-oriented cognition (i.e., processing stimuli in the performance of the ongoing task), and especially, the dovetailing of the two.

This explanation has the potential to explain many of the findings relating to performance of different forms of PM task. For instance, one might think in these terms when hypothesizing about the processing differences made by (a) time-based PM tasks (when no clock is available) versus event-based PM tasks, and (b) between time-based tasks where a clock is not available and the same task where a clock is available. In the former cases of both examples there is an increased need to maintain a stimulus-independent representation (e.g., a continually updated representation of the passage of time) and therefore considerable switching between this mode of attending and stimulus-oriented attending, as required by the ongoing task. By comparison, in the latter examples one might expect relatively increased attendance to information available in the environment; that is, stimulus-oriented attending.

However we are at such an early stage of our understanding both of PM and of the functions of BA 10 that this must remain a hypothesis at present. In particular, although our experimental findings have emphasized a medial/lateral BA 10 functional distinction, the results from our meta-analyses suggest that there are additional functional distinctions to be made in BA 10 along a rostral-caudal dimension, and that this may relate somehow to the varying demands that PM tasks make on retrospective memory versus executive control processing. Moreover, we have yet to discover how the processes supported by BA 10 that we suggest are involved in PM may also be used in the furtherance of other behaviors. For instance: (a) our lab has also shown substantial BA 10 activations that are provoked by context memory paradigms, and these seem to show anatomical overlap with some of those activated by both PM and SI/SO attentional switching paradigms (Simons, Gilbert, Owen, Fletcher, & Burgess, 2005; Simons, Owen, Fletcher, & Burgess, 2005), and (b) prospective memory failures do not seem to be the only symptom shown by patients with rostral prefrontal cortex damage. Clearly we still have a great deal to learn. However, progress both in our understanding of the experimental and motivational psychology of PM, and also in the neuroscience of PM, has been so rapid over the last 10 years that there must be considerable hope for our future understanding of this important human behavior, and how the brain supports it. Moreover, it seems increasingly likely that progress in both fields will go hand-in-hand.

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