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The role of rostral prefrontal cortex in prospective memory: A voxel-based lesion study

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ABSTRACT

Patients with lesions in rostral prefrontal cortex (PFC) often experience problems in everyday-life situations requiring multitasking. A key cognitive component that is critical in multitasking situations is prospective memory, defined as the ability to carry out an intended action after a delay period filled with unrelated activity. The few functional imaging studies investigating prospective memory have shown consistent activation in both medial and lateral rostral PFC but also in more posterior prefrontal regions and non-frontal regions. The aim of this study was to determine regions that are necessary for prospective memory performance, using the human lesion approach. We designed an experimental paradigm allowing us to assess time-based (remembering to do something at a particular time) and event-based (remembering to do something in a particular situation) prospective memory, using two types of material, words and pictures. Time estimation tasks and tasks controlling for basic attention, inhibition and multiple instructions processing were also administered. We examined brain-behaviour relationships with a voxelwise lesion method in 45 patients with focal brain lesions and 107 control subjects using this paradigm. The results showed that lesions in the right polar prefrontal region (in Brodmann area 10) were specifically associated with a deficit in time-based prospective memory tasks for both words and pictures. This deficit could not be explained by impairments in basic attention, detection, inhibition or multiple instruction processing, and there was also no deficit in event-based prospective memory conditions. In addition to their prospective memory difficulties, these polar prefrontal patients were significantly impaired in time estimation ability compared to other patients. The same region was found to be involved using both words and pictures, suggesting that right rostral PFC plays a material nonspecific role in prospective memory. This is the first lesion study showing that rostral PFC is crucial for time-based prospective memory. The findings suggest that time-based and event-based prospective memory might be supported at least in part by distinct brain regions. Two particularly plausible explanations for the deficit rest upon a possible role for polar prefrontal structures in supporting in time estimation, and/or in retrieving an intention to act. More broadly, the results are consistent with the view that the deficit of rostral patients in multitasking situations might at least in part be explained by a deficit in prospective memory.

1. Introduction

The term "mystery" was used by Mesulam (Mesulam, 1986; see also Burgess, Alderman, Volle, Benoit, & Gilbert, 2009) to describe the behaviour of patients with frontal lobe damage who showed intact performance on traditional neuropsychological assessment of intellectual ability, memory, language, motor skills, perception, and problem-solving, but at the same time showed strong disturbances in everyday life. In the last 20 years, several hypotheses have been proposed in order to explain the problems experienced by these patients (Burgess, 2000; Duncan, Burgess, & Emslie, 1995; Shallice & Burgess, 1991). Burgess, Shallice and collaborators have attempted formal quantification of the difficulties experienced by these patients in everyday life. They designed specific tests to identify a deficit in relatively ill-structured situations (i.e. requiring participants to organise their own behaviour rather than following specific instructions), and identified a specific brain region where damage was associated with these problems: rostral prefrontal

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cortex (rostral PFC) or frontopolar cortex (Bird, Castelli, Malik, Frith, & Husain, 2004; Burgess, 2000; Burgess et al., 2009; Burgess, Veitch, de Lacy Costello, & Shallice, 2000; Shallice & Burgess, 1991).

More specifically, rostral prefrontal patients may exhibit difficulties when there are several possible ways to behave, when the behaviour is not fully guided by the environment (i.e. what to do and when to act have to be decided by the person), and when two or more tasks have to be engaged alternately, by interleaving. Preparing a meal, or shopping, are typical examples of real-life situations that make these demands. Situations of this type have been labelled as requiring "multitasking" (Burgess et al., 2000). Problems with multitasking can now be assessed with specific neuropsychological tests such as the Six Element Test, the Greenwich test or the Multiple Errands Test (Burgess, Alderman, Evans, Emslie, & Wilson, 1998; Burgess et al., 2000, 2009; Shallice & Burgess, 1991). In a lesion study of 60 patients, using the Greenwich test (Burgess et al., 2000), Burgess and collaborators concluded that rostral patients "*did not do what they intended to do*, despite being able to learn the task rules, form a plan, remember their action, and say what they should have done". In other words, these patients appeared mainly impaired in the 'intentional' component of multitasking. In cognitive psychology, the processes that allow the realisation of an intention after a delay are gathered in the concept of "prospective memory" (Meacham & Dumitru, 1976).

Prospective memory is defined as the ability to carry out a delayed intended action. It refers to a type of memory that allows maintaining and retrieving future plans, goals and activities, which is a crucial ability for human everyday life. Two types of prospective memory can be considered: time-based and event-based (Harris, 1984; Kvavilashvili & Ellis, 1996; for a review see McDaniel & Einstein, 2007). Time-based prospective memory consists of remembering to do something at a particular time, for example remember the meeting with Paul at 5 pm. Event-based prospective memory consists of remembering to do something in a particular situation. For instance, remember to ask Paul for his book next time I meet him.

Experimental testing tries to imitate these real life situations, asking subjects to maintain an intention while doing something else – called the ongoing task – and to retrieve this intention at the appropriate moment, determined either by time or by a given situation.

The few functional imaging studies that have been performed using such tasks (Burgess, Quayle, & Frith, 2001; Burgess, Scott, & Frith, 2003; Gilbert, Gollwitzer, Cohen, Burgess, & Oettingen, 2009; Okuda et al., 1998, 2007; den Ouden, Frith, Frith, & Blakemore, 2005; Reynolds, West, & Braver, 2009; Simons, Scholvinck, Gilbert, Frith, & Burgess, 2006) have shown consistent activation in rostral PFC (in Brodmann area [BA] 10), but also in more posterior prefrontal regions and in non frontal regions. It therefore appears that the rostral PFC is often activated by prospective memory tasks. But are patients with rostral frontal lesions impaired in these tasks?

Functional imaging cannot formally demonstrate whether a region is critical for a task or a function. Lesion studies are thus necessary to indicate for which tasks and processes rostral PFC functioning is necessary. This approach is all the more important because functional imaging studies have shown hemodynamic changes in rostral PFC in many different cognitive paradigms (Christoff & Gabrieli, 2000; Ramnani & Owen, 2004), such as those involving memory retrieval (Simons, Owen, Fletcher, & Burgess, 2005), working memory (Owen, McMillan, Laird, & Bullmore, 2005; Volle et al., 2005), branching and task switching (Braver & Bongiolatti, 2002; Koechlin, Basso, Pietrini, Panzer, & Grafman, 1999; Koechlin & Hyafil, 2007), relational integration (Christoff et al., 2001; Kroger et al., 2002; Reynolds, McDermott, & Braver, 2006), reasoning (Bunge, Wendelken, Badre, & Wagner, 2005; Green, Fugelsang, Kraemer, Shamosh, & Dunbar, 2006; Green, Kraemer, Fugelsang, Gray, & Dunbar, 2010; Volle, Gilbert, Benoit, & Burgess, 2010), and even in simple attention tasks (Pollmann, 2001) or during rest or daydreaming (Buckner, Andrews-Hanna, & Schacter, 2008; Gilbert, Dumontheil, Simons, Frith, & Burgess, 2007; Gusnard & Raichle, 2001; Mason et al., 2007). New techniques for lesion studies, such as voxel-by-voxel lesion-deficit mapping allow precise clinical–radiological correlations by testing all damaged voxels. They do not rely upon classifying patients into categorical groups or choosing a cut-off for pathology, in contrast with more classical methods (Baier et al., 2010; Bates et al., 2003; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004; Frank, Damasio, & Grabowski, 1997; Gläscher et al., 2009; Kinkingnehun et al., 2007; Tyler, Marslen-Wilson, & Stamatakis, 2005; Rorden & Karnath, 2004; Volle et al., 2008). Instead, statistical tests are performed at each voxel or cluster of voxels, by considering patients damaged in that voxel and comparing them to control values. Because of this voxel-by-voxel testing, and because patients' lesions are analysed within the same template as fMRI studies, these new lesion methods give results more comparable to functional imaging ones. Yet the lesion approach has rarely been used to explore the cerebral correlates of prospective memory, and there is little evidence showing the critical regions for prospective memory (Burgess et al., 2008).

Therefore, we conducted a lesion study in 45 patients with focal brain lesions, carefully screened for potential confounding cognitive deficits, using a voxel-based method, combined with both time- and event-based prospective memory tasks.

2. Materials and methods

The experiment was approved by the local research ethics committee. All participants were able to provide written, witnessed, consent.

2.1. Subjects (see Table 1 with patients' details)

Patients were recruited mainly from the Neurosurgery and the Neurological Departments of King's College Hospital, London, UK. Additional patients were recruited from two other London hospitals: the Regional Neurological and Rehabilitation Unit of the Homerton University Hospital and the Wolfson Rehabilitation Centre, St. George's Healthcare Trust, Wimbledon. Sixty-seven patients were assessed, when attending for a full investigation of their lesion, if they met the following criteria. (i) The presence of a cerebral focal lesion was confirmed by an anatomical CT scan or MRI, available for the current condition. (ii) The lesion was acquired in adulthood (mostly haemorrhage, ischemic stoke or brain tumour; see Table 1). (iii) Participants were able to understand and perform the cognitive tasks. Patients who demonstrated gross disorientation or visual, memory, reading, naming or instrumental impairments that would interfere with the tasks were excluded (impairments detected on VOSP perception battery, on Shortened Revised Token Test (De Renzi & Faglioni, 1978), on the National Adult Reading Test – NART (Bright, Jaldow, & Kopelman, 2002; Nelson & O'Connell, 1978) and on McKenna confrontation naming test (McKenna & Warrington, 1983), on Warrington's recognition memory test (Warrington, 1984)). (iv) Patients had no prior history of neurological or psychiatric disease requiring hospitalisation, of alcohol or other substance abuse, or of developmental problems. (vi) All included patients were right-hand dominant and had English as their first language. It is important to note that every patient who matched the above criteria was included, regardless of the location of the lesion or the pattern of the cognitive deficit. Of the 67 tested, full data including brain scans were eventually available for 45 patients.

Fig. 1 shows the location of lesions of these 45 patients. Lesions were located as follows. Twenty patients had a lesion that did not involve the frontal lobes, (i.e. 'Non Frontal'), but involved temporal (11 patients), parietal (6 patients) and subcortical areas (3 patients). Twenty five patients had a lesion that involved the frontal lobes, among which 8 involved the rostral prefrontal region ('Rostral PF'; approximately Brodman area 10 [BA10]), and 17 were prefrontal but not rostral ('Posterior PF': 6 premotor, 4 dorsolateral prefrontal, 6 ventrolateral and 1 orbitoventral lesions).

Normative data was acquired from a group of 107 healthy normal subjects matched for age, gender and estimates of their basal (or pre-morbid for the patients) IQ, based on tests of irregular word reading (either the National Adult Reading Test – NART (Nelson & O'Connell, 1978), or the Wechsler Test of Adult Reading – WTAR (Wechsler, 2001; see Table 1)). In this control group, subjects were right-handed, native English speakers; they had no history of neurological or psychiatric disease, and were capable and willing to take part in the experiment. Patients were compared to controls using a voxel-based approach.