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Prospective memory in thalamic amnesia

G.A. Carlesimo[a,b,*], A. Costa[b], L. Serra[c], M. Bozzali[c], L. Fadda[a,b], C. Caltagirone[a,b]

[a] Neurology Clinic, Tor Vergata University, Rome, Italy
[b] Unit of Clinical and Behavioral Neurology, Santa Lucia Foundation, IRCCS, Rome, Italy
[c] Neuroimaging Laboratory, Santa Lucia Foundation, IRCCS, Rome, Italy

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ABSTRACT

The contribution of the thalamus to the functioning of prospective memory (PM) is currently unknown. Here we report an experimental investigation of the performance of two patients with bilateral infarcts in the anterior-mesial regions of the thalami on an event-based PM paradigm. One patient, G.P., had a pervasive declarative memory impairment but no significant executive deficit. The other patient, R.F., had a memory deficit limited to verbal material with associated behavioral abnormalities (inertia and apathy); she performed poorly on tests of executive functions. Although both patients performed poorly on the PM task, a qualitative analysis of performance revealed different mechanisms at the base of their impaired PM. G.P. had reduced declarative memory for target words compared with normal controls; but, unforgotten words were normally able to elicit his recall of the prospective intention. Conversely, R.F.'s declarative memory for target words was as accurate as that of normal controls, but she presented a dramatically reduced ratio between the number of target words she recalled and the number of times she activated the prospective intention on the PM task, suggesting that her deficit consisted of difficulty in activating the intention despite normal declarative memory for the target events. In conclusion, results of the present study demonstrate that thalamic structures have an important role in PM processes. They also document that damage to the anterior-mesial regions of the thalami affects PM abilities by two different mechanisms, respectively based on the relative disruption of declarative memory or executive processes functioning, which, in turn, is related to the specific intrathalamic structures involved by the lesions. Indeed, while G.P.'s pervasive declarative memory deficit was underlain by bilateral involvement of the mammillo-thalamic tract, R.F.'s executive and behavioral abnormalities were likely related to bilateral damage of the midline, intralaminar, and medio-dorsal nuclei.

1. Introduction

Prospective memory (PM) is generally defined as the cognitive ability (or set of cognitive abilities) that enables an individual to carry out a previously planned action at the appropriate time (Einstein & McDaniel, 1996; Ellis & Kvavilashvili, 2000). Over the last few years, there has been an increasing interest in PM among neuropsychologists. Both observational and experimental studies in clinical populations have reported that PM is particularly vulnerable to brain damage. In fact, it has been found impaired in a variety of neurological and psychiatric conditions, such as closed head injury (Carlesimo, Casadio, & Caltagirone, 2004; Fleming et al., 2008; Groot, Wilson, Evans, & Watson, 2002), Parkinson's disease (Costa, Peppe, Caltagirone, & Carlesimo, 2008; Kliegel, Phillips, Lemke, & Kopp, 2005), preclinical (Kazui et al., 2005; Troyer & Murphy, 2007) and early Alzheimer's disease (Huppert & Beardsall, 1993), and schizophrenia (Wang et al., 2009).

Many different experimental paradigms have been proposed for laboratory-based investigations of PM. According to Burgess, Scott, and Frith (2003), an experimental paradigm suitable for PM investigation should fulfill the following criteria: (i) subjects under assessment should be first informed that at the occurrence of a specific event (event-based task) or at the expiration of a given time (time-based task) they are expected to carry out some action; (ii) the delay period between creating the intention and occurrence of the appropriate time to act (the socalled "retention interval") is filled with activities known as the "ongoing task", which prevents continuous, conscious rehearsal of the intention over the entire delay period; and (iii) the retrieval context (time expiration or event occurrence) does not interfere with, or directly interrupt, performance of the ongoing task; under these conditions, intention enactment is self-initiated.

It is still being debated whether and to what extent the cognitive abilities involved in remembering to perform a previously planned action overlap with or differ from those implicated in more

* Corresponding author at: IRCCS S. Lucia, V. Ardeatina, 306, 00179 Rome, Italy. Tel.: +39 06 51501517; fax: +39 06 51501388.
E-mail address: memolab@hsantalucia.it (G.A. Carlesimo).

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traditional assessments of retrospective memory (which assess the ability to remember previous events or previously acquired information). In fact, PM tasks share with retrospective memory tasks the need to encode, maintaining over time and successively retrieving some new information (e.g., a word list in a retrospective memory task or the trigger time or event in a PM paradigm, and the specific actions to be performed). However, a critical difference between these two experimental conditions is that, unlike retrospective memory tasks in which the examiner prompts the experimental subjects to initiate retrieval of studied items, in a typical PM task subjects have to rely exclusively on their own initiative to start an intended action in response to a trigger time or event. This implies that two cognitive components are critical for the correct delayed execution of planned actions: (i) a more typical prospective component, which allows subjects to reactivate the intention at the appropriate time or when the cue event occurs, without any explicit external prompt and (ii) a retrospective memory component, which allows subjects to effectively encode and remember the cue event or time together with the particular actions to be performed (Ellis, 1996; Kvavilashvili, 1987). It is generally acknowledged that the retrospective component of a PM task relies on the same declarative memory system also involved in the encoding and successive retrieval of past events. Conversely, a number of cognitive abilities (some of which are still underspecified) contribute to the effective functioning of the prospective component (Burgess & Shallice, 1997; Guynn, McDaniel, & Einstein, 1998; Kvavilashvili, 1987; Marsh, Hicks, & Landau, 1998). Planning, attentional, time monitoring, and set-shifting abilities, as well as motivational factors, are all implicated in reactivating the prospective intention at the appropriate time. Some of these abilities are considered part of the executive system.

The role of executive or declarative memory abilities in mediating PM processes has been confirmed by neuropsychological studies of both healthy elderly subjects and patients with brain damage. For example, in a study by McDaniel, Glisky, Rubin, Guynn and Routhieaux (1999), a group of 41 healthy elderly individuals, divided into 4 experimental groups on the basis of their performance on tests of executive functions and declarative memory, were submitted to an event-based PM task. The authors found that subjects with higher functioning executive abilities showed better prospective remembering than those with lower functioning executive abilities. Conversely, they found no significant difference in performance on the PM task which could be attributed to reduced declarative memory functioning (see McFarland & Glisky, 2009, for analogous results). Instead, the hypothesis that performance on the prospective and retrospective components of a PM task mainly relies on executive functions and declarative memory abilities, respectively, is supported by the results of a previous study by our group involving 16 patients suffering from chronic sequelae of severe closed head injuries (Carlesimo et al., 2004). In that study, we reported a strict association between accuracy in the spontaneous retrieval of intention (i.e., the prospective component of the PM task) and performance on the Wisconsin Card Sorting Test. Conversely, accuracy in remembering the specific actions to be performed (i.e., the retrospective component) was related to performance on tests of anterograde declarative memory, such as free recall of a word list and a short story.

The different reliance of retrospective and prospective components of PM on declarative and executive abilities suggests that the same brain regions that subserve these cognitive abilities are also directly implicated in PM. In this perspective, it has been suggested that the mesial areas of the temporal lobes, whose role in declarative memory is well established, might support the retrospective component of memory, whereas the frontal lobes, more involved in executive functions, might support its prospective component (Adda, Castro, Além-Mar e Silva, de Manreza, & Kashiara, 2008; Carlesimo et al., 2004; Poppenk, Moscovitch, McIntosh, Ozcelik, & Craik, 2010). The contribution of neuropsychology to the search for the anatomical basis of PM has thus far been rather scanty. In a study by Burgess, Veitch, de Lacy Costello, and Shallice (2000), 60 patients with circumscribed cerebral lesions were administered a multitasking procedure that included the assessment of event-based PM functioning. On the basis of structural equation modeling, these authors concluded that the left anterior and posterior cingulate gyri are both implicated in retrospective memory demands, whereas left BA 8, 9, and 10, together with the right dorso-lateral prefrontal cortex, support processes of PM and planning functions. Involvement of the mesio-temporal regions in PM functioning was, instead, supported by a study comparing performances on event-based and time-based PM tasks of 26 patients with right hippocampal sclerosis, 22 patients with left hippocampal sclerosis, and 26 matched controls (Adda et al., 2008). Overall, the patients performed significantly worse than the healthy controls on both PM tasks. Moreover, the patients with left-sided hippocampal sclerosis performed worse than those with right-sided involvement on the event-based task. No doubt richer has been the contribution of functional neuroimaging at clarifying the neural substrates of PM. Using PET, Okuda et al. (1998) found that the rostral, dorso-lateral, and mesial regions of the frontal lobes were more activated when subjects performed an event-based PM task than when they were involved in a verbal span task. Although these authors identified a specific region of activation in the left parahippocampus, they did not speculate on the potentially different roles of frontal and mesiotemporal circuits in the processing of prospective and retrospective components of the PM task. Subsequent studies emphasized the role of the most rostral region of the frontal lobes (broadly corresponding to BA 10) in maintaining the delayed intention during a PM task (e.g., Burgess, Quayle, & Frith, 2001; Burgess et al., 2003). In the most recent functional imaging study on this topic, Poppenk et al. (2010) reported that activations in left prefrontal BA 10 and in the right parahippocampal gyrus were directly correlated with subjects' performances on an event-based PM task. These authors explicitly acknowledged the crucial contribution of these cortical areas involved in executive and declarative memory functions in supporting the prospective and retrospective components of PM.

In this paper, we report the results of a study investigating the role of the human thalamus in PM functioning. A role of the thalamus in PM can be hypothesized based on the above mentioned roles of declarative memory and executive functions in normal PM functioning, Indeed, in the context of a complex and multifaceted contribution of the thalamus to cognition, the domains in which the role of the thalamus is most documented are declarative memory and executive functions. In a series of papers, Van der Werf, Witter, Uylings, and Jolles (2000) and Van der Werf et al. (2003) established that a clear relationship exists between deficits of these two main cognitive domains and well localized lesions of the thalamus. Concerning declarative memory, these authors demonstrated unequivocally that a focal thalamic lesion can produce a hippocampal-like amnesic syndrome only when the mammillo-thalamic tract (MTT) is involved. In fact, in a review of the literature (Van der Werf et al., 2000) they documented that the MTT was lesioned in virtually all reported cases of individuals who became amnesic following a thalamic infarct. In another study, which reported the results of a neuropsychological investigation of 22 new cases with focal thalamic lesions, the overlap and subtraction image analysis revealed a close association between the presence of an amnesic syndrome and damage in an area of the ventral anterior region of the left thalamus, coinciding with the location of the MTT (Van der Werf et al., 2003). It is widely accepted that a lesion to the MTT, which directly connects the mammillary bodies to the anterior thalamic nuclei, may produce an amnesic syndrome because of its critical position in the declarative mem-