**Deficits in prospective memory following damage to the medial subdivision of the mediodorsal thalamic nucleus.**

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**Abstract**

Identifying the neurocognitive mechanisms that lead individuals remembering to execute an intention at the right moment (prospective memory, PM) and how such mechanisms are influenced by the features of that intention is a fundamental theoretical challenge. In particular, the functional contribution of subcortical regions to PM is still unknown.

This study was aimed at investigating the role of the medial subdivision of the mediodorsal thalamic nucleus (mMDT) in PM, with particular focus on the processes that are mediated by the projections from/to this structure. We analyzed the performance of a patient (OG) with a right-sided lesion involving the mMDT in a series of PM tasks that varied for focality (i.e., overlapping of processes for the PM and ongoing tasks) and emotional valence of the stimuli, comparing the patient’s performance with that of a control group.

We found that the mMDT damage led to deficits in PM that were modulated by focality and emotional valence. OG indeed showed: a greater cost in the ongoing performance when a nonfocal PM task was added; a slowing down in retrieving the intentions, in particular when these were associated with focal PM cues; an abnormal performance in the task with positive PM cues.

Our findings provide evidence of a contribution of mMDT to PM and suggest a modulation of prefrontal-dependent strategic monitoring and a possible interaction with the limbic structures in the integration of emotion and PM processes. They also give support to the still controversial idea that connections with the perirhinal cortex mediate familiarity-based recognition.

**Keywords:** prospective memory; mediodorsal thalamus; focality, emotion; recognition;

**Introduction**

Prospective memory (PM) is the ability to remember to execute intended actions at the appropriate time in the future, such as remembering to take medication on time, or to stop at the gas station on our way home.

A particular challenge for succeeding in PM is that the intended action has to be accomplished while we are simultaneously engaged in other activities, called ongoing tasks (Einstein & McDaniel, 1990). PM involves both a retrospective component (recollection or cued-recall of episodic information) and a prospective component (e.g., Burgess & Shallice, 1997). The retrospective component consists in storing and maintaining the associative link between a given time or event (i.e., the PM cue) and the intention to execute, and in remembering the content of such intention, thus it represents the “what” knowledge of declarative memory. The prospective component includes executive processes, such as planning when to perform the action at the right time, actively rehearsing the PM intention, monitoring the environment for the PM cue, and shifting from the ongoing task to activation of the PM intention (Kliegel, Brandenberger, & Aberle, 2010).

Furthermore, multiple processes can be differentially recruited to accomplish PM tasks, depending on the features of the task itself. Some kinds of PM task are mediated by spontaneous retrieval of the intention, whereas other kinds of PM tasks require strategic monitoring as they involve top-down attentional and memory processes to monitor for the presence of the PM cues in the environment and to maintain/rehearse the intention in memory (Cona et al., 2015a; Einstein et al., 2005; Guynn, 2003). In laboratory settings, the presence of strategic monitoring is testified by decline in ongoing performance (lower accuracy and slower reaction times) when a PM instruction is added to the ongoing task (i.e., ‘PM cost’) (Guynn, 2003; Smith, 2003).

Multiple factors were shown to modulate the extent to which individuals rely upon spontaneous retrieval or strategic monitoring to perform PM tasks (Einstein et al., 2005). Among these, focality of the PM task plays a central role (Scullin et al., 2010). In focal PM tasks, the PM cue is processed as part of the ongoing task (e.g., keeping words in working memory while remembering to press a button whenever a specific word appears; Einstein & McDaniel, 1990); whereas in nonfocal tasks, processing of the PM cue does not overlap processing of the ongoing stimuli (e.g., keeping words in working memory while remembering to press a button whenever the background of the screen shows a particular pattern). According to the multiprocess view, spontaneous retrieval is more likely to occur in focal PM tasks, whereas strategic monitoring is required mainly in nonfocal PM tasks (Einstein et al., 2005). Also, the recognition of the PM cue seems to occur automatically, on the basis of familiarity processes, in focal tasks, whereas it requires more effortful and controlled resources in nonfocal PM tasks (Cona et al., 2014).

Emotional valence of the PM cue is another relevant dimension capable to modulate PM processes. For example, an event-related potential (ERP) study demonstrated that, as compared with neutral cues, emotional PM cues are more prone to elicit automatic, bottom-up, capture of attention and spontaneous retrieval of the associated intention, and can also boost a greater engagement of top-down attentional and memory processes needed to hold the attention and to retrieve the intention from mind (Cona et al., 2015b).

The multifaceted nature of PM is reflected in the widespread number of brain regions involved and differently recruited depending on the features of the PM task. In particular, according to a recent model - the Attention to Delayed Intention (AtoDI) model - the dorsal frontoparietal network supports strategic monitoring as mediates top-down attentional and episodic memory processes. On the other hand, the ventral frontoparietal network subserves mainly the retrieval processes, as it mediates the bottom-up attention, which is “captured” both externally, by the PM cue, and internally, by the associated intention stored in memory (Cona et al., 2015a; 2016). Nonfocal tasks were shown to engage preferentially dorsal frontoparietal regions such as dorsolateral prefrontal cortex (DLPFC), superior parietal lobe and precuneus, as well as control-related structures as the anterior cingulate cortex. Focal PM tasks rely instead more upon ventral structures such as inferior parietal lobule and posterior cingulate cortex (Cona et al., 2016; McDaniel et al., 2013).

As far as the authors are aware, no first study has ever investigated the effect of emotional valence of the PM task on the specific brain activations associated with performing it.

Furthermore, in contrast to the well-established role of frontoparietal networks in PM, the role of medial temporal structures and other subcortical regions has been less explored, leading to mixed and still inconclusive results (e.g., Adda et al., 2008; Cona et al., 2015a; Gordon et al., 2011). In particular, the investigation of brain activation-behavior associations carried out in the study by Poppenk and collaborators (2010) revealed that activations in right parahippocampal gyrus and left frontopolar regions predicted the success in a PM task. In the study by Gordon et al. (2011), the authors explored brain structure–behavior associations in healthy and very mildly memory impaired older adults and found a positive correlation between medial temporal volume and accuracy on a focal PM task, whereas such relationship was not observed for nonfocal PM task.

A neuropsychology study by Adda et al. (2008) evidenced a PM impairment in patients with hippocampal sclerosis, suggesting a critical role of hippocampus in PM. In contrast, two recent meta-analyses did not show consistent activations in hippocampal regions across the neuroimaging studies on PM (Cona et al., 2015a, 2016). These studies found instead a consistent activation of thalamus, even if a clear interpretation of its functional meaning is still lacking.

Only two studies so far directly explored the specific involvement of the thalamus in PM, providing results that are difficult to reconcile (Carlesimo, Costa, Serra, Bozzali, Fadda, & Caltagirone, 2010; Cheng, Tian, Hu,Wang,Wang, 2010).

Cheng et al. (2010) found that as compared with healthy controls, patients with thalamic stroke were impaired to remember PM intentions only when these were associated with a given time (time-based PM task) and not when associated with a particular event/cue (event-based PM task). The authors did not however report the exact intrathalamic localization of the lesions, thus it was not possible to clarify the specific contribution of the intrathalamic regions to PM.

A better specification of the lesion was instead provided by the study by Carlesimo et al. (2010), where the PM performance was assessed in two patients (‘GP’ and ‘RF’) presenting lesions of medio-dorsal (MD) thalamic nuclei. Patient GP’s damage was mainly confined to the mammillo-thalamic tract (MTT) bilaterally and only marginally included the reuniens nucleus, which is one of the midline nuclei. On the other hand, patient RF’s lesions included the left MTT and the reuniens nucleus, the parafascicularis and central-median nuclei (in the intralaminar nuclei), and the ventral part of the MD nucleus. Both the patients showed impaired event-based PM performance, but the mechanisms underlying such impairment were different, and depend on the thalamic divisions affected. It was attributable to a deficit in declarative memory in patient GP and to a deficit in executive functions in patient RF.

The heterogenic function of this region has been demonstrated by studies outside the PM contexts, which revealed that MD thalamic nuclei are crucial for memory processes, learning, executive functions, reward and decision-making (see Carlesimo, Lombardi, Caltagirone, & Barban, 2015; Mitchell, 2015, and Vertes, Linley, & Hoover, 2015 for recent reviews). Several studies carried out by Edelstyn and collaborators (2012, 2014, 2016) on a patient – OG – with a right-sided medial MD (mMD) thalamic lesion revealed that such lesion was associated with impairment in familiarity-based processes contributing to recognition memory as well as deficits in allocating attentional and executive control resources. In particular, the study by Edelstyn et al. (2016) demonstrated a dissociation between a deficient familiarity-based recognition and spared recollection in OG. The authors interpreted this result in line with the dual-process view, which states that recollection is mediated by the hippocampus and its associated structures (i.e., the fornix, the anterior thalamic nucleus, the MTT and the mammillary bodies), whereas familiarity-based recognition relies on a separate network of regions that includes the perirhinal cortex and the mMDT (Aggleton & Brown, 1999, 2006; Yonelinas et al., 2010).

The aim of our study was to better elucidate the specific contribution of the medial MD thalamus (mMDT) to PM by exploring the performance in several PM tasks enrolling the same patient (OG) who participated to the studies by Edelstyn and collaborators (2012, 2014, 2016). This allowed us to have a very detailed, previously documented, neuropsychological profile, which helped us to fully interpret our findings in the context of the literature.

Importantly, we designed our study and developed the hypotheses basing not only on the mMDT nucleus itself, but also taking into account the projections from/to mMDT nucleus, as it represents a higher order relay structure (Mitchell, 2015).

First, mMDT is strongly reciprocally linked to prefrontal cortex (PFC), especially the medial, insular and orbital prefrontal regions (Petrides and Pandya, 2007; Hoover and Vertes, 2011). Previous studies showed indeed that mMDT functions significantly overlap with those of the PFC (Edelstyn et al., 2014; Block, Dhanji, Thompson-Tardif, Floresco, 2007; Mitchell and Chakraborty, 2013). In particular, the study by Edelstyn et al. (2014) found that, on test of vigilance and attention, OG’s performance was spared under conditions of low demand but not when the same paradigms were repeated under conditions of high demand, thus conditions requiring more executive control resources. Short-term memory and working memory also were spared under all but the conditions that most demanded executive control. Based on this body of evidence, we hypothesized that mMD thalamic lesions might impact PM performance by influencing strategic monitoring, which entails top-down controlled attentional and memory resources allocated to monitor the environment for the presence of the PM cue and to refresh the intention in mind. To test this hypothesis, we adopted two PM tasks: a focal and a nonfocal PM task, previously used in the study by Cona et al. (2014). As strategic monitoring is involved with a greater extent in nonfocal PM task than focal PM task, we expected to find a greater cost (i.e., decline in ongoing performance when a PM task is added) in nonfocal task. Important for our aims, if the mMD thalamus subserves strategic monitoring, a greater cost should be evidenced in OG patient with respect to the control group and should be coupled with a decline in nonfocal PM performance in OG.

Second, we expected to find an impairment more in the focal PM task than in the nonfocal task. This hypothesis is based on the idea that focal PM tasks rely more upon bottom–up capture of attention and familiarity-based recognition than nonfocal tasks do (McDaniel, Umanath, Einstein, & Waldum, 2015; Cona et al., 2014, 2016), thus performance within the nonfocal task should show higher levels of sparing.

Furthermore, as these processes were shown to be recruited selectively in the retrieval phase, when the PM cue appears, they are not reflected in the ‘monitoring’ cost in the ongoing task (Cona et al., 2015a; 2016; McDaniel, Lamontagne, Beck, Scullin, & Braver, 2013). Consequently, we expected that the impairment in focal task should dissociate from spared concurrent ongoing performance.

These expectations are also based on three converging lines of evidence: *i)* neuroanatomical studies show that the mMDT receives afferent projections from the perirhinal cortex (Saunders, Mishkin, Aggleton, 2005); *ii)* imaging studies of healthy volunteers show activation of the perirhinal cortex and the thalamus during bottom-up capture of attention (Iaria et al., 2008); and *iii)* both lesion studies of patients and imaging studies of healthy volunteers show that familiarity memory depends on the perirhinal cortex and mMDT (Bowles et al., 2011; Carlesimo et al., 2015; Edelstyn et al., 2016; Kafkas & Montaldi 2012,2014; Kafkas et al., 2017; Martin et al., 2011; Montaldi et al., 2010; but see Pergola et al., 2013).

Third, mMDT is strongly interconnected with limbic subcortical and cortical structures, receiving afferents from the anterior cortical, basolateral and basomedial nuclei of the amygdala, and ventral tegmental area (VTA) (see Vertes, Linley, & Hoover, 2015 *for a review*). Therefore, we expected that mMDT lesions lead to impaired performance in tasks including emotional PM cues, leaving PM less affected when the intention was associated with neutral PM cues. To test this hypothesis, we used emotional PM tasks previously developed by Cona et al. (2015b), in which participants were required to remember accomplishing an intended action that could be associated either to positive, negative, or neutral cues.

**Materials and Methods**

**The patient and the healthy controls**

Patient *OG* is a right-handed male of high average intelligence (IQ, 116, *The National Adult Reading Test,* Nelson & Willison, 1991) and was aged 78 years at the time of testing. He formally worked as an electrical engineer before retiring in 2000. He continues to enjoy an active life-style, spending time playing bridge, cooking for himself and his wife, walking and caring for his grand-children. *OG* has a 30-year history of visual migraine and hypertension, prior to suffering an ischemic stroke in 2000. The patient’s initials have been changed to preserve anonymity.

A group of 12 healthy men was matched to OG for age (mean age = 71.5; SD= 5.21; t = 1.19; p = .25) and premorbid IQ (mean score = 117.38; SD = 3.38; t = - 0.39; p = .70). This study was part of an ongoing program of study, approved by the Ethics Committee and was conducted in accordance with good clinical practice (European Medicines Agency, 2002).

**Neuropsychological profile**

*Executive function, arousal and attention, short-term and working memory*

Evidence of executive dysfunction was present for tasks of response initiation and response suppression (*Hayling Tests*), and more demanding tasks reliant on the ability to plan, sequence, organize and monitor information for problem-solving (*Brixton Test of Spatial Anticipation, phonetic and semantic fluency*) (see Edelstyn et al., 2014 for further details). Under conditions where attentional demand was low, OG performed in the normal range (auditory vigilance, visual vigilance, auditory selective attention, and visual selective attention; Simple Flexibility task, covert attention, left and right “valid cue”). However, on the more demanding versions of these same tasks, OG’s performance was impaired: bimodal vigilance, divided attention, Complex Flexibility and covert attention (left “invalid-valid cue” conditionand right “invalid-valid cue” condition) (Test for Attentional Performance, Zimmermann & Fimm, 1995) (see Edelstyn et al., 2014 for further details).

OG shows spared short-term storage (WMS forward digit span, forward spatial span) and working memory (reverse digit span, reverse spatial span) although there was evidence of a task specific working memory decline using a more demanding switching paradigm (letter/number sequence) (see Edelstyn et al., 2014 for further details).

*Declarative memory*

OG has a material-specific memory deficit: Impairments are limited to visual memoranda and are evident for several stimulus categories (unfamiliar faces, abstract shapes, doors), modes of retrieval (recall, forced-choice recognition, familiarity assessment but not recollection of episodic details during yes/no recognition), short and extended retention intervals (The Rey Complex Figure Test, 3-min and 15-min recall; Doors and People Test, DPT, Shapes recall subtest; familiarity-based recognition of unfamiliar faces; DPT forced choice recognition of doors).

On the other hand, no abnormalities are evident in verbal long-term memory (Wechsler Memory Scales, WMS, Logical memory immediate and delayed recall; DPT People cued recall and Names forced-choice recognition subtests) (see Edelstyn et al., 2012 and Edelstyn et al., 2016 for further details).

**Structural Brain Imaging**

*Lesion mapping*

Patient OG has a unilateral, right-sided lesion, centred on the magnocellular subdivision of the mediodorsal thalamic nucleus (Figure 1). The lesion extends laterally, cutting across the central MDT, the parvicellular MDT (MDc, MDpc, respectively), the internal medullary lamina (IML), a white matter tract positioned between the MDT and ventral thalamus, the (rostral) central lateral intralaminar nucleus, that resides within the IML, and the ventrolateral thalamus. The paraventricular and central-medial midline thalamic nuclei, and the mammillo-thalamic tract are also affected.

*Volumetric measurement*

The absolute measures of OG’s left and right mammillary bodies, left and right hippocampus, left and right perirhinal cortex areas were all within normal range although there was evidence of dilation of both left and right lateral ventricles (see Edelstyn et al, 2012 and Edelstyn et al, 2014 for details of image acquisition, techniques of lesion mapping and reconstruction). The horizontal and coronal sections of OG’s lateralised thalamic lesion shown in Figure 1 below are reproduced with permission.

**Experimental PM sessions**

**Focal/ Nonfocal PM paradigm**

A modified version of the tasks used by Cona et al. (2014) was used (Figure 2).

The PM task consists in remembering to accomplish a pre-specified intention (i.e., pressing a key of the pc keyboard, in our experiment) when a particular stimulus, the PM cue, occurs on the screen. Two are the peculiar features that make a PM task: 1) the prospective intention needs to be performed while the individual is engaged in other ongoing tasks, and 2) the PM cue associated with the intention to remember has to occur rarely, otherwise the paradigm would become a dual-task or a task-switching paradigm.

In our paradigm, the ongoing task was a lexical decision task. In this task, white strings of letters occurred in the center of a black screen, one at a time. Half the participants responded by pressing the “M” key with their right index finger when the string was a word, and the “N” key with the right middle finger when the string was a nonword. The reverse mapping was assigned to the other half of participants. All participants were asked to respond as quickly and as accurately as possible. In the baseline session, the ongoing task was performed alone (i.e., there was no additional PM task), and was always administered first.

In the PM sessions, participants were asked to perform also a PM task, which consisted in pressing the “C” key (instead of the keys for the ongoing task) when a PM cue occurred on the screen. In the focal PM task, the PM cues were particular target words (e.g. “candle”). In the nonfocal PM task, the cues were words belonging to given categories, such as “daisy” for the category “flower” or “salmon” for the category “fish”. The psycholinguistic variables of words (mean length and mean frequency) were matched across the different experimental conditions (focal, nonfocal, and baseline blocks) and stimulus types (ongoing words and PM cues).

Sixty word/nonword stimuli were used for the baseline session. Both the focal and nonfocal sessions comprised 200 stimuli, with 12 PM cues included among these. Each of the PM sessions was divided in 10 blocks of 19 ongoing stimuli and 1 PM cue each. In one of the blocks, the PM cue occurred twice, in order to prevent participants from no longer monitoring after the first appearance of the PM cue. PM cues differed across the blocks of the PM sessions. Each block was preceded by the encoding phase, during which a specific word (in focal PM session) or a category (in nonfocal PM session) was presented for 3000 ms.

Before performing the experimental sessions, participants familiarized with the lexical decision task (12 trials), receiving feedbacks about RTs and accuracy of their performance after each trial.

**Emotional PM paradigm**

A shorter version of the paradigm used in the study by Cona et al. (2015b) was adopted (Figure 2). The PM task consisted in remembering to press a pre-defined key when a pre-specified positive, negative, or neutral picture (the PM cue) occurred on the screen while participants were engaged in a concurrent, ongoing activity. The ongoing task was a one-back working memory task comprising pictures with different emotional valence as well, as it included neutral (e.g., a building, a spoon), pleasant (e.g., a delicious cake, a puppy), and unpleasant pictures (a tornado, a crying child). The pictures were selected from the International Affective Picture System IAPS (Lang et al., 2005). The arousal value did not differ between pleasant and unpleasant pictures. Stimuli were presented in the center of a black screen.

In the baseline session, the one-back task was performed alone. Participants were asked to decide whether the picture occurring on the screen was the same or different from the picture that occurred one trial before, by pressing one of two possible response keys with the right index or middle finger (“N” or “M” keys). The response-key mapping was counterbalanced across participants. On each trial, the stimulus occurred on the screen for 2000 ms or until a response was made, followed by a a fixation cross that pseudorandomly lasted 1200, 1400, or 1600 ms.

The paradigm was composed of three PM sessions, which differed for the emotional valence of the PM cue (unpleasant, neutral, pleasant). Participants had to remember to press the “Z” key with their left index finger, instead of making the one-back response, whenever a PM cue was presented. Within each PM session, pleasant, unpleasant and neutral ongoing pictures were pseudo-randomly presented, whereas the PM cue valence was kept constant.

Each of the PM sessions included 100 ongoing stimuli and 10 PM cues, divided in two blocks. PM cue was never also a one-back hit trial. The blocks were preceded by the encoding phase, during which five PM cues were presented, one at a time, in the center of the screen for 3000 ms, followed by 1000 ms of blank screen. Before the PM sessions, participants practiced with the ongoing task, performing 24 ongoing trials of practice (8 trials per valence).

**Results**

Statistical comparisons between patient and healthy controls were run using Crawford and Garthwaite’s (2002) test to compare the individual patient scores (accuracy and reaction times (RTs)) with those of the control sample. False Discovery Rate (FDR) correction was applied for multiple comparisons to prevent Type I error (rejection of a true null hypothesis). Figures 3 and 4 show the most representative results. All the results are reported in Tables 1.

**Focal/Nonfocal PM paradigm**

*Performance on the PM task*

Performance accuracy on the PM task did not significantly differ between OG and the controls, either in the focal session (OG: mean = 0.92; Controls: mean = 0.90; SD = 0.11; t = 0.09; p > .05) or in nonfocal session (OG: mean = 0.83; Controls: mean = 0.82; SD = 0.10; t = 0.19; p > .05).

Importantly, as can be seen in Figure 3, OG showed slower PM responses in both focal (OG: mean = 1804 ms; Controls: mean = 835 ms; SD = 107; t = 8.69; p < .0001) and nonfocal session (OG: mean = 1263; Controls: mean = 934; SD = 226; t = 2.71; p = .02). The impairment, however, seems to be more evident in the focal session, as testified by the larger value of patient’s z-score for focal PM response latencies (*z* = 9.05) than for nonfocal responses latencies (*z* = 2.83).

*Performance on the Ongoing task*

As shown in Table 1, performance accuracy on the ongoing task was not significantly different between OG and the controls in the baseline condition, thus when the lexical decision task was executed alone (words: t = 0.32; nonwords: t = 0.68; p*s* > .05). In contrast, OG showed an impairment in the ongoing performance in the focal and nonfocal conditions, selectively for the nonwords (nonwords in focal condition: t = - 3.36; p = .036; nonwords in nonfocal condition: t = - 2.40; p = .05).

Likewise, RTs did not differ between OG and controls in the baseline session (words: t = - 0.56; nonwords: t = - 0.76; p*s* > .05) or in the focal session (words: t = 1.36; nonwords: t = 1.63; p*s* > .05). On the contrary, as shown in Figure 3, OG showed a slowing down of RTs relative to controls in the nonfocal session (words: t = 3.37; p = .036; nonwords: t = 2.90; p *=* .04).

**Emotional PM paradigm**

*Performance on the PM task*

As can be seen in Figure 4, OG showed impaired PM performance selectively for intentions associated with positive PM cues (t = - 4.13; p = .003), whereas the PM performance in negative and neutral sessions did not differ as compared to controls (t = -.28 and t = -.38, respectively; ps > .05, see Figure 4 and Table 1).

OG had slower PM responses relative to controls, in all the three valence conditions (Negative: t = 5.03; Neutral: t = 5.74; Positive: t = 3.41; all ps < .01).

*Performance on the Ongoing task*

As for the lexical decision task in the focal/nonfocal paradigm, we did not find any difference between OG and controls in this ongoing task (i.e., the N-back task) in the baseline session, regardless of the valence of the N-back stimuli (Negative ongoing stimuli: t = -1.20; Neutral ongoing stimuli: t = 0.01; Positive ongoing stimuli: t = -1.28; all ps > .05). On the other hand, OG was significantly impaired in the ongoing task specifically in the positive session, thus when he had to perform the Nback task together with remembering to perform an intention associated with pre-specified positive PM cues (Positive PM session: t = - 4.80, ps < .01). No difference in the ongoing performance between OG and controls was observed either for the negative or neutral session (both ps > .05).

Concerning the RTs, no difference was observed in the ongoing task during baseline session, either for negative, neutral or positive stimuli (all ps > .05). In contrast, OG showed slower RTs in the ongoing task during all the PM sessions (negative PM session: t= 3.95; neutral PM session: t = 2.48; positive PM session: t = 2.48; all ps < .05), thus when two tasks were simultaneously executed.

**Discussion**

The aim of this study was to investigate the role of the mMDT in PM, with particular focus on the functional implications of the disconnection of projections from/to this structure. We analyzed the PM performance in a patient with a right-sided lesion involving the mMDT and the central medial midline nucleus.

The main findings are that mMDT is causally involved in PM functioning and that damage to this structure leads to deficits in PM that are modulated by several factors, such as focality and emotional valence of the PM task. More specifically, the key behavioral findings can be summarized as follow: *i*) OG showed a greater cost in the ongoing performance as compared to the control group when a PM task was added, especially when the PM task was nonfocal; *ii*) OG showed a slowing down in retrieving the intentions, in particular when these were associated with focal PM cues; *iii*) OG showed an abnormal performance in the positive PM session: OG displayed a lower level in both PM accuracy and ongoing accuracy when the PM intentions were carried out in relation to positive PM cues. This pattern of deficits was instead absent in neutral and negative PM sessions.

The OG’s increased PM cost in the ongoing task of the nonfocal condition seems to be due to his difficulties in executive control and attentional systems that support strategic monitoring, which is typically more required for nonfocal tasks. Edelstyn et al. (2014) stated indeed that damage to OG's mMDT and intralaminar nuclei makes his attentional and executive systems less effective, leading, in turn, to deficits in high-demand attention and executive function conditions but normal performance in the low-demanding conditions. OG's neuropsychological profile evidenced in the focal/nonfocal PM paradigm is consistent with this view. As clearly highlighted by Figure 3, indeed, the slowing down of RTs shown by OG increased as a function of the PM+ongoing paradigm demands. More specifically, we did not find any difference between OG and controls in the ongoing task when this task was performed alone, or when the patient had to judge word string in focal condition. These indeed were low-demanding conditions. By contrast, the greatest difference was observed for nonword stimuli in nonfocal conditions, therefore in the most difficult condition, which required the greatest amount of attentional and controlled resources to: 1) monitor whether the stimulus was a PM cue or not; 2) maintain active in mind two rules (one for the lexical decision task and the other for the PM task); 3) inhibit the PM intention in favor of the ongoing response. The present result supports also the findings of the study by Carlesimo et al. (2010) (RF’s case), who showed that damage to midline, intralaminar, and MD nuclei affected PM abilities by disruption executive processes functioning. Our finding is noteworthy as it demonstrates that mMDT crucially contributes to strategic monitoring. A hypothesis is that mMDT interplays with the prefrontal cortex in adjusting the top-down attentional and executive processes depending on the task rules and PM intentions.

When looking at the PM performance, we found that OG took longer than controls in performing the PM intentions, and this was particularly evident for the focal PM task.

This result might be explained by the anatomical connection of the mMDT with the perirhinal cortex (Saunders et al., 2005), which mediates bottom-up processes being part of the ventral pathway (Iaria et al., 2008). In such a way, it corroborates the idea that, at the retrieval phase, the PM cue elicits a bottom-up capture of attention, and this process is triggered particularly in focal conditions (Cona et al., 2015a; 2016).

Another possible reason why OG showed deficits in the focal PM task is the association of mMDT with familiarity-driven processes, as shown by previous studies of episodic memory (Edelstyn et al., 2016; see also Aggleton and Brown, 1999). In fact, the study by Edelstyn et al. (2016) highlighted a dissociation between a deficient familiarity-based recognition and spared recollection in OG.

This result thus corroborates the dual-process view, which states that only recollection is reliant on the hippocampus and associated structures, whereas familiarity, and the recognition processes that depend on it, are mediated by other regions, such as the perirhinal cortex and the mMDT (Aggleton & Brown, 1999, 2006; see also Yonelinas et al., 2010).

In the context of PM, our result fits well with the noticing plus search theory (Einstein & McDaniel, 1996), which stated that, in some conditions, the occurrence of a PM cue can elicit a sense of familiarity (i.e., noticing) that leads, in turn, to a consciously controlled search of memory to establish the meaning of the PM cue and retrieve the content of the associated intention from memory. Thus, noticing is thought to be a relatively automatic familiarity-based process that supports the detection of a PM cue. Importantly, such process is more commonly triggered by focal PM cues than nonfocal PM cues, as evidenced by a recent event-related potential (ERP) study (Cona et al., 2014). Familiarity-based process seems to be very likely to occur in the focal condition of our paradigm where the same word was presented in both the encoding phase and the retrieval phase.

However, since a slowing down in PM responses was observed also in the nonfocal task even if to a lesser extent, we can argue that the familiarity-based processes cannot be the only mechanism underlying OG’s deficits. As also pointed out by Carlesimo et al. (2010), executive dysfunction may interfere not only with strategic monitoring but also with fulfillment of PM intention itself, for many reasons, including (i) deficits in binding processes required to create the cue-intention association; (ii) deficits in the controlled process of memory search and in the active, effortful, retrieval; (iii) deficits of attentional resources that would interfere with execution of a dual task; (iv) deficits in rule shifting that would interfere with the switch between the ongoing and the PM response; and (v) general inertia that interferes with execution of previously programmed intentions.

In particular, with regard to a possible contribution of the mMDT to rule shifting, Block et al. (2007) proposed that mMDT would inform the mPFC to switch task rule, and the mPFC, consequently, inhibits the current task to execute the task based on the new rule. Applying this idea to the PM paradigms, it is possible that once a PM cue occurs, mMDT informs the mPFC to shift from the ongoing task rule to the PM task rule. Based on the mMDT signal, the mPFC would then inhibit the ongoing responses in order to accomplish the PM intention. Future studies, perhaps using high temporal resolution techniques such as ERPs, would be helpful to better highlight the exact executive control-related mechanism accounting for the PM impairment in nonfocal task.

Finally, a very interesting (and somehow surprising) result is that OG showed a selective deficit in carrying out intentions that were associated with positive PM cues. Moreover, OG had a lower level of accuracy in ongoing task, but again, only when he had to strategically monitor for positive PM cues and maintaining in memory intentions related to these cues.

Previous studies demonstrated that amygdala interacts in concert with the orbitofrontal cortex and the mMDT to quickly assess and transfer emotionally relevant stimuli to the cortex (Zikopoulos & Barbas, 2012; for reviews, see Ghashghaei, Hilgetag, Barbas, 2007; Barbas, 2007). A disconnection of these pathways that are responsible for the integration of emotional and cognitive processes could likely cause the impairment observed in positive PM task.

In particular, a possible reason for the selective deficit in the PM tasks comprising positive PM cues is the fact that the mMDT works together with the amygdala and orbitofrontal cortex to mediate reward-based decision making (Izquierdo & Murray, 2000). Importantly, a recent meta-analysis revealed that the MDT was consistently activated by erotic, monetary and food rewards (Sescousse, Caldú, Segura, & Dreher, 2013). Another meta-analysis showed that MDT activity was stronger before (thus in anticipation) than during the reward outcome (Knutson and Greer, 2008). Such anticipatory responses were interpreted as reflecting increased attention towards motivationally relevant or salient stimuli. Similar kinds of stimuli (i.e., erotic, monetary and food) were included in our task, thus they might have elicited the involvement of thalamic-PFC-amygdala system for their meaning closely associated with reward/pleasure.

Furthermore, OG’s lesion also encroached paraventricular thalamic midline nuclei (PVT), which project to nucleus accumbens (other than to the amygdala and medial prefrontal cortex). The PVT and nucleus accumbens are sensitive to pleasant stimuli, being implicated in hedonic and motivational aspects of rewards (Colavito et al., 2015, Cardinal and Everitt, 2004; Pecina and Berridge, 2005).

To our knowledge, ours is the first study to report deficits in processing information related to positive stimuli after thalamic damage. Notably, taken together, these results demonstrate that mMDT and the inter-connected regions (i.e., the PFC regions and limbic structures) support PM performance by subserving the prospective component/executive mechanisms of PM, emotion-cognition integration processes and likely, familiarity-based recognition processes. Finally, in line with the multiprocess view (Einstein, & McDaniel, 2005), we showed that the involvement of these structures in PM is modulated by multiple factors, such as focality and emotional valence of the PM cue.

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**Figure Legends**

**Figure** **1**. The upper panel shows four horizontal MR slices (thickness 1 mm), highlighting that OG's lesion is lateralized to the right thalamus, and involves parts of the paralamellar, the parvicellular and the magnocellular subdivisions of the dorsal medial thalamus. The slices (left to right) are at 7.2 mm (slice 1), 5.4 mm (slice 2), 4.5 mm (slice 3), and 3.6 mm (slice 4) dorsal of the dorso-ventral plane (0 mm).

The lower panel shows a magnification of the thalamic region from each of the 4 MR slices. The parvicellular (MDpc), magocellular (MDmc) and paralamellar (MDpl) subdivisions of the DMT, the central lateral (CL) intralaminar nucleus, together with the central medial (CeM), and paraventricular (Pv) midline nuclei are indicated using a series of overlays from Morel (2007). Notes: the midline is indicated in blue, in Figure 1 lower. R, right of mid-line.

**Figure 2. Schematic illustration of the PM paradigms**

The left panel displays examples of trials in focal and nonfocal PM paradigm. The right panel shows an example of the trials occurring in the emotional PM paradigm. In this example, the PM cue was a positive stimulus (the balloons). Note: The pictures illustrated in the figure are not those used in the study (taken from the IAPS database), but are taken from Internet only for illustration purposes.

**Figure 3.** **Performance in the Focal/Nonfocal PM paradigm.** The left panel shows that OG had a worse performance with respect to the control group in both the PM tasks, but especially in the focal conditions. The right panel highlights that OG had slower ongoing responses than the control group, selectively in the nonfocal condition.

(BAS\_W= words in the baseline; BAS\_NW= nonwords in the baseline; NONFOC\_W= words in the focal session; FOC\_NW= nonwords in the focal session; FOC\_W= words in the nonfocal session; NONFOC\_NW= nonwords in the nonfocal session). The error bars represent standard error. The *asterisks* indicate significant differences.

**Figure 4.** **Performance in the Emotional PM paradigm.**

OG displayed a worse performance in both the PM task (left panel) and the ongoing task (right panel), selectively in the positive condition. The error bars represent standard error. The *asterisks* indicate significant differences.

**Table 1. Performance of OG patient and the control group**

|  |  |  |
| --- | --- | --- |
| Focal/Nonfocal Pm paradigm | OG patient | Control group (N= 12) |
| PM task |  |  |
| Focal PM acc | 0.92 | 0.90 (0.1) |
| Nonfocal PM acc | 0.83 | 0.82 (0.1) |
| Focal PM RTs | 1804 | 835 (107) |
| Nonfocal PM RTs | 1263 | 934 (116) |
|  |  |  |
| Ongoing Task |  |  |
| *ACC* |  |  |
| Baseline words | 1.00 | 0.99 (0.03) |
| Baseline nonwords | 1.00 | 0.95 (0.07) |
| Focal words | 0.97 | 0.98 (0.06) |
| Focal nonwords | 0.91 | 0.98 (0.02) |
| Nonfocal words | 0.97 | 0.96 (0.06) |
| Nonfocal nonwords | 0.92 | 0.97 (0.02) |
| *RTs* |  |  |
| Baseline words | 715 | 840 (212) |
| Baseline nonwords | 865 | 1019 (193) |
| Focal words | 1086 | 890 (119) |
| Focal nonwords | 1214 | 973 (141) |
| Nonfocal words | 1445 | 977 (133) |
| Nonfocal nonwords | 1480 | 1003 (158) |
|  |  |  |
| Emotional PM paradigm | **OG patient** | **Control group (N= 12)** |
| PM task |  |  |
| Negative PM acc | 0.90 | 0.93 (0.1) |
| Neutral PM acc | 0.90 | 0.94 (0.1) |
| Positive PM acc | 0.50 | 0.93 (0.1) |
| Negative PM RTs | 1689 | 1023 (127) |
| Neutral PM RTs | 1594 | 926 (112) |
| Positive PM RTs | 1355 | 973 (107) |
|  |  |  |
| Ongoing task |  |  |
| *ACC* |  |  |
| Baseline negative stimuli | 0.89 | 0.94 (0.04) |
| Baseline neutral stimuli | 0.98 | 0.98 (0.02) |
| Baseline positive stimuli | 0.93 | 0.97 (0.03) |
| Negative session – Neg stimuli | 0.90 | 0.91 (0.10) |
| Negative session – Neu stimuli | 0.82 | 0.92 (0.09) |
| Negative session – Pos stimuli | 0.91 | 0.93 (0.09) |
| Neutral session – Neg stimuli | 0.98 | 0.94 (0.05) |
| Neutral session – Neu stimuli | 0.93 | 0.93 (0.06) |
| Neutral session – Pos stimuli | 0.94 | 0.97 (0.04) |
| Positive session – Neg stimuli | 0.79 | 0.96 (0.04) |
| Positive session – Neu stimuli | 0.80 | 0.96 (0.04) |
| Positive session – Pos stimuli | 0.78 | 0.98 (0.03) |
| *RTs* |  |  |
| Baseline negative stimuli | 1013 | 732 (141) |
| Baseline neutral stimuli | 907 | 721 (132) |
| Baseline positive stimuli | 949 | 712 (112) |
| Negative session – Neg stimuli | 1315 | 866 (85) |
| Negative session – Neu stimuli | 1169 | 877 (122) |
| Negative session – Pos stimuli | 1316 | 850 (103) |
| Neutral session – Neg stimuli | 1221 | 856 (114) |
| Neutral session – Neu stimuli | 1228 | 921 (133) |
| Neutral session – Pos stimuli | 1120 | 885 (115) |
| Positive session – Neg stimuli | 1146 | 855 (112) |
| Positive session – Neu stimuli | 1181 | 865 (103) |
| Positive session – Pos stimuli | 1093 | 861 (133) |
|  |  |  |

*Note: In the control group column, psychometric means and standard deviations (in parenthesis) are reported.*