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TESI

Mental (future) event construction: component processes, neural bases, and role in decision making.

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ABSTRACT

The present thesis addresses the cognitive and neural mechanisms underlying the complex act of constructing mental events and its role in decision-making. A specific form of mental event construction, namely the imagination of future events (or episodic future thinking), has been a topic of intense inquiry, due to its purported adaptive role. Episodic future thinking shares underlying cognitive and neural mechanisms with episodic remembering, which has fuelled the discussion on its core component processes, and those of mental event construction in general. To this aim, different theories have been advanced, focussing on the reconstructive nature of past memories, which can be flexibly recombined into novel experiences, the self-projection into alternative situations that underlies most forms of mental simulations, or the mental construction of scenes, seen as the backbones of either past, future and atemporal experiences. The first chapter of this thesis delves into the relation between episodic memory and episodic future thinking, investigating multiple facets of future thinking in a patient with focal retrograde amnesia, and reveals that episodic remembering is crucial for episodic future thinking, less so for other forms of mental simulation for which semantic memory suffices, or for future-oriented decision making. The second chapter begins to explore the neural bases of mental future event construction in patients with damage to the ventromedial prefrontal cortex (vmPFC), and confirms a deficit in episodic future thinking in vmPFC patients, while excluding that this deficit depends on impairments in working memory or narrative abilities. The third chapter investigates whether a deficit in constructing (single) scenes may underly vmPFC patients' event construction impairment, studying scene construction and processing in vmPFC patients and comparing them to hippocampal patients, to investigate the different roles that vmPFC and hippocampus play in the construction of scenes. The chapter ends with a proposed model of the interaction of vmPFC and the hippocampus in which vmPFC initiates scene and event construction, and the hippocampus help build cohesive scenes. Lastly, the fourth chapter explores the adaptive role of episodic future thinking, showing that externally cueing episodic future thinking in vmPFC patients reduces their steep discounting of future rewards, which further elucidates the role of vmPFC in mental event construction and in guiding future-oriented choice.

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Chapter 3.

INTRODUCTION

1. Relationship between episodic memory and episodic future thinking

Episodic memory is part of the long-term, declarative memory system (Squire, 1992) and it has been originally defined as memory for personally experienced, autobiographical, past events (Tulving, 1972). Episodic memory is quasi-experiential, because its memories have all of the features of the ongoing experience, namely spatiotemporal structure, perspectivity and modality-specific sensory information, and event specific, because it contains information about what happened, when, and where (so-called "WWW information"), related to a single spatiotemporal context (Conway, 2009; Mahr & Csibra, 2018). The re-experience of past events enables individuals to "travel in time", namely to travel back to personal past experiences and to consciously recollect what happened in the past from a first-hand perspective (Tulving, 1999; Mahr & Csibra, 2018). This is possible because episodic memory is the only type of memory having access to the autonoetic consciousness (i.e., self-knowing), defined as "the kind of consciousness that mediates an individual's awareness of his or her existence and identity in subjective time extending from the personal past through the present to the personal future" (Tulving, 1985).

A autonoetic consciousness is the crucial feature that distinguishes episodic memory from other forms of memory. Semantic memory, the abstract knowledge of the world stored in the long-term, declarative memory system, has access to the noetic consciousness (i.e., knowing) of retrieving general information from memory, in the absence of a feeling of personally re-experiencing the past (Tulving, 1972; Tulving, 1985). Procedural memory, implicit information stored in the long-term, non-declarative memory system, is characterized by anoetic consciousness (i.e., non-knowing), because stored information is retrieved without explicit awareness (Tulving, 1985). According to this view, any form of knowledge or skill stored in semantic or procedural memory, when is used, is oriented to the present and aims to improve individual's interaction with the current environment, without the need of retrieving how the knowledge/skill was acquired; on

the contrary, event-related information stored in episodic memory, when is used, is oriented to the past and the awareness of how the information was acquired on a specific occasion allows not only the conscious retrieval of the event itself, but also a re-experience of it (Tulving, 1999). The mental re-experience of past events enables the recollection of the qualitative, contextual information associated to them with the same vividness, richness and specificity experienced during the event itself (Tulving, 2002).

In the last decade, it has been suggested that episodic memory allows to mentally travel through subjective time toward both the past and the future (Tulving, 1985, 1999). Mentally projecting the self into the future to pre-experience an event by simulating it in one's own mind has been conceptualized as "episodic future thinking" (EFT; Atance & O'Neill, 2001) or "prospection" (Gilbert & Wilson, 2007). The simulation of personal future episodes allows individuals to envision contextual information associated to scenarios never experienced before and to predict their consequences (Atance & O'Neill, 2001; Gilbert & Wilson, 2007). These simulated scenarios can have high vividness, richness and specificity, which make them characterized by a strong feeling of pre-experience of the future event, similar to that associated to the re-experience of a real past event (Tulving, 1985, 1999; Atance & O'Neill, 2001). Importantly, the act of imagining personal future experiences has been conceptualized as inextricably built upon that of consciously remembering personal past experiences, as I will highlight below. The ability to mentally travel in time and consciously simulate past and future scenarios enables individuals to anticipate and plan for future contingencies, transcending current needs and motivational states (Suddendorf & Corballis, 2007), and has been claimed to distinguish humans from other species (Tulving, 1999; Atance & O'Neill, 2001; Gilbert & Wilson, 2007).

From this first conceptualization of the relationship between episodic memory and episodic future thinking, it emerges that two core elements are shared by both abilities, namely the self and the subjective time (Tulving, 1999, 2002; Klein, 2013). Successive investigations have agreed with the idea that the projection of the self in time distinguishes episodic future thinking from other

forms of future simulation (Atance & O'Neill, 2001, 2005), and that self-consciousness, the capacity to think about the one's own mental states and focus the attention on one's own inner experience (Scheier & Carver, 1985), may have a role in accessing autobiographical information and transforming it into the subjective experience of "travelling through time" to pre-experience a particular future episode (Suddendorf & Corballis, 2007; D'Argembeau et al., 2010).

Although this traditional view has associated future-oriented mental time travel almost exclusively with episodic memory (Tulving, 1985, 1999, 2002), more recent approaches have acknowledged the role that also semantic memory plays for the simulation of the future (reviewed in Klein, 2013). Atance & O'Neill (2001) have suggested that a semantic knowledge regarding the future, called "semantic future thinking" (Atance & O'Neill, 2001) runs in parallel to episodic future thinking, and that the level of novelty of the simulated event influences and determines the type of component – more semantic or more episodic – that will be used during the simulation of the future (Atance & O'Neill, 2005). According to this view, a semantic, script-based knowledge of the future is more likely to be used to simulate familiar, routine, events; whereas, an episodic representation of the future is required to anticipate events that are more novel and uncertain (Atance & O'Neill, 2005). The idea that the type of information used and, consequently, the type of simulation experienced, episodic or semantic, is related to the nature of the future events itself and to task demands (Klein, 2002, 2013), has been widely accepted and has led some authors to conclude that the contribution of episodic and semantic elements to future simulation invariably depends upon the accessibility of information that is relevant to the event of interest (Szpunar, 2010), in line with the heuristic principle that the content of any future simulation reflects the information that is most readily accessible (Kahneman & Tversky, 1982).

Recent experimental investigations have specified the role of semantic memory during the simulation of the future, showing that during the construction of EFT, both episodic, detailed elements, and semantic, more abstract, information are accessed and used to create mental events. In particular, when individuals construct specific future (as well as past) events, they firstly access

and activate general, abstract personal knowledge (i.e., personal semantic information and/or general events), and then they produce episodic details relevant for a specific event. Thinking about personal goals especially facilitates the access to episodic information and the generation of the specific event (D'Argembeau & Mathy, 2011). Therefore, the imagination of future events can be seen as a protracted generative process entailing different levels of specificity, where abstract knowledge, drawn from semantic memory, provide a context to guide the retrieval, integration and interpretation of specific episodic details, drawn from episodic memory (D'Argembeau & Mathy, 2011). Both episodic and semantic memory are necessary to engage in EFT and, in general, to travel in time (Klein, 2013), and abstract, conceptual knowledge offered by semantic memory works as a "scaffold" which enables the (re)construction of both past and future events, by providing appropriate schemas or abstract representation to melt together episodic details and give them the personal significance of an extended mental event (Irish, Addis, Hodges, & Piguet, 2012; Irish & Piguet, 2013).

A considerable number of studies in the last decades has been focused on the important similarities between episodic memory and episodic future thinking, highlighting their cognitive and neural overlap, which will be explained in the next paragraphs.

1.1 Cognitive overlap between episodic memory and episodic future thinking

The emerging insights about the profound tie between episodic memory and episodic future thinking have been proved by a growing evidence of a striking cognitive similarity during the act of remembering past experiences and that of imagining future episodes (see Schacter et al., 2012 for a review). Experimental manipulations of psychological factors, such as the emotional content or the temporal distance, have been shown to affect the recollection of the past and the imagination of the future in a comparable way. Positive events elicit greater subjective re-experiencing for past events and pre-experiencing for future events than negative events; temporally close events in either the past or the future contain more sensory and contextual details and enhance greater feeling of re-

experiencing or pre-experiencing than temporally distant events (D'Argembeau & Van der Linden, 2004). Furthermore, individual differences in visual imagery ability and emotion regulation strategies have similar effects on both past and future events. Individuals with better visual imagery abilities experience more sensory details during both the recollection of past events and the imagination of future events; similarly, individuals used to suppress emotions as a regulation strategy recollect past events and imagine future events with fewer sensory, contextual and emotional details (D'Argembeau & Van der Linden, 2006). On the contrary, individuals with high self-efficacy, who believe that they can cope effectively with events, remember past events and imagine future events with more episodic details than do individuals with low self-efficacy (Brown, Dorfman, Marmar, & Bryant, 2012). Also, individual differences in the generation of self-defining memories are mirrored by those in self-defining future projections (D'Argembeau, Lardi, & Van der Linden, 2012), and cognitive functions outside the memory domain similarly affect the generation of past and future events. For instance, measures of executive functioning are correlated with the number of episodic details provided during the recollection of past events and the imagination of future events, suggesting that executive processes, such as the organization, access and monitoring of retrieved autobiographical information, play a similar role during the generation of events in both temporal directions (D'Argembeau et al, 2010).

Commonalties between past and future thinking also emerge across the life span. Children develop the ability to report and make judgments about personal past and future events at a similar age, between three and five years (Busby & Suddendorf, 2005; Russell, Alexis, & Clayton, 2010; Hayne & Imuta, 2011), even though episodic future thinking (compared to remembering) has a protracted developmental trajectory (Ghetti & Coughlin, 2018). Older adults, on the other hand, produce fewer internal – episodic details and more external – semantic details than younger adults both when they remember the past and when they imagine the future (Addis, Wong, & Schacter, 2008; Addis, Musicaro, Pan, & Schacter, 2010; Gaesser, Sacchetti, Addis, & Schacter, 2011).

However, cognitive differences also exist between remembering the past and imagining the future. For instance, remembered events are associated with increased retrieval of sensory-perceptual details compared to imagined future events (D'Argembeau & Van der Linden, 2004; Berntsen & Bohn, 2010) or imagined events in general (Johnson, Suengas, Foley, & Raye, 1988), and contain more specific information or more episodic details than imagined future experiences (Addis, Wong, & Schacter, 2008; Addis, Musicaro, Pan, & Schacter, 2010). Furthermore, some cognitive functions differently affect the generation of past and future events. For instance, imagining future events compared to remembering past events, relies more on executive functions (Johnson, Suengas, Foley, & Raye, 1988; D'Argembeau & Van der Linden, 2004). Visuospatial constructive abilities, self-consciousness and future orientation are correlated with the number of sensory details reported during the imagination of future events, but not during the recollection of past events (D'Argembeau et al, 2010). These findings are consistent with the idea that imagining a specific future event engages more intensive constructive activity than remembering past event, necessary to flexibly recombine multiple past details into a novel episode (Schacter & Addis, 2007). I will come back to this point later.

1.2 Neural overlap between episodic memory and episodic future thinking

The cognitive commonalities between remembering the past and imagining the future are reflected in their neural substrates, as shown by findings coming from functional neuroimaging (fMRI) and neuropsychology.

Evidence from neuroimaging

fMRI evidence has showed that episodic memory is supported by a distributed network of brain regions, which includes areas consistently activated across episodic – autobiographical memory imaging studies and therefore referred to as the "core" of the autobiographical memory network, namely, the medial and ventrolateral prefrontal cortices, the medial and lateral temporal cortices, the lateral parietal cortex, the retrosplenial and posterior cingulate cortex, and the

cerebellum. The network also includes areas less consistently activated and referred to as "secondary" to the core of the autobiographical memory network, comprising the dorsolateral prefrontal cortex, superior medial and superior lateral cortex, anterior cingulate, medial orbitofrontal, temporopolar and occipital cortices, and the thalamus and amygdala (Maguire, 2001; Maguire & Frith, 2003; Svoboda, McKinnon, & Levine, 2006; Cabeza & Jacques, 2007; Addis, Wong, & Schacter, 2007). Importantly, fMRI studies show that imagining personal future events activates areas that overlap substantially with the episodic – autobiographical memory network, including medial temporal and prefrontal cortex, posterior cingulate and retrosplenial cortex, and lateral parietal and temporal areas (Okuda et al., 2003; Addis, Wong, & Schacter, 2007; Szpunar, Watson, & McDermott, 2007; Botzung, Denkova, & Manning, 2008; Spreng, Mar, & Kim, 2009). This set of brain areas active during the generation of both past and future events also overlaps with the "default mode network" (Raichle et al., 2001), a set of areas mainly active during passive cognitive states (i.e., resting quietly with closed or open eyes), when individuals shift their attention inward, without engaging in any specific goal-directed behaviour (Raichle et al., 2001). Coherently, the brain default network is activated by active cognitive tasks that encourage internal mentation, like episodic memory and episodic future thinking (Buckner, Andrews-Hanna, & Schacter, 2008).

The functional anatomy of the default mode network has been further investigated to show that it comprises a core system hub, namely, the posterior cingulate cortex and anterior medial prefrontal cortex, as well as two subsystems that interact with the core: a "dorsal medial prefrontal cortex (dMPFC) subsystem", including dMPFC, temporoparietal junction, lateral temporal cortex, and temporal pole, and a "medial temporal lobe (MTL) subsystem", comprising ventral MPFC, posterior inferior parietal lobule, retrosplenial cortex, parahippocampal cortex, and hippocampal formation (Andrews-hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). These two subsystems are functionally dissociated, such that the dMPFC subsystem is preferentially activated when individuals are focussed on their present mental states and make self-relevant, affective decisions, whereas, the MTL subsystem is preferentially engaged when individuals are focussed on their

future mental states and make decisions involving the construction of a mental scene based on memory (Andrews-hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010). Importantly, aspects of both subsystems are recruited by autobiographical memory and spontaneous cognition (Andrews-Hanna, Saxe, & Yarkoni, 2014).

Despite important similarities in the neural bases of past and future event simulation, neuroimaging findings have shown some discrepancies between remembering the past and imagining the future, reflecting the differences observed at cognitive level. The imagination of future events is associated to greater neural activity in frontopolar regions and hippocampus compared to the recollection of past events (Okuda et al., 2003; Addis, Wong, & Schacter, 2007; Szpunar, Watson, & McDermott, 2007), and this greater activity for future events is mainly evident during the initial construction phase of the event (e.g. the generation of the event in response to a cue). Importantly, while the initial construction of future events uniquely engages the right hippocampus, possibly as a response to the novelty, the subsequent elaboration of future events is characterized by a remarkable overlap of activity in regions of the autobiographical memory retrieval network (Addis, Wong, & Schacter, 2007). Furthermore, imagining events activates the anterior hippocampus, medial prefrontal cortex and inferior frontal gyrus, whereas remembering past events rich in contextual and visuospatial details preferentially engages posterior hippocampus, parahippocampal gyrus and regions of posterior visual cortex (Addis, Pan, Vu, Laiser, & Schacter, 2009). The increased activity found associated to future relative to past events is in line with the idea that the imagination of future events requires more demanding constructive processes, needed to extract details from memory and to recombine them into novel scenarios. This explanation fits with theoretical accounts suggested to elucidate the relationship between episodic memory and episodic future thinking, as described next.

Evidence from neuropsychology

These neuroimaging findings have been confirmed by neuropsychological evidence, showing that nodes of the core brain network are not only associated to, but also necessary for

simulating both past and future experiences. Although early neuropsychological investigations of the famous case H.M. (Scoville & Milner, 1957; Corkin, 2002), who became amnesic as a result of a surgical treatment of epilepsy, had clearly shown that a damage to the medial temporal lobes (MTLs) cause a serious impairment in the ability to form new lasting autobiographical memories, only almost three decades later neuropsychology has begun to study the relationship between amnesia and future thinking. Endel Tulving (1985) showed that the patient K.C., suffering from a severe retrograde and anterograde amnesia as a result of a widespread damage to the MTLs due to a car accident, was unable to recollect any personal event of his past as well as to imagine any personal episode in his future, even in the near one (e.g., tomorrow). K.C.'s past and future episodic impairment was dissociated from his intact semantic knowledge of the world and about himself (Tulving, 1985; Rosenbaum, Kohler, et al., 2005; Rosenbaum, Gilboa, Levine, Winocur, & Moscovitch, 2009). Another amnesic case, patient D.B. (Klein, Loftus, & Kihlstrom, 2002), showed that the dissociation between (impaired) episodic and (spared) semantic memory evident in the recollection of the past is extended to the simulation of the future, with the patient unable to imagine personal future events, but capable to imagine non-personal – public – future events (Klein et al., 2002). Further investigations have confirmed that the severity of episodic, but not semantic, autobiographical memory loss is accounted for by the degree of hippocampal damage in patients with MTL amnesia (Rosenbaum et al., 2008). The inability of amnesic patients with MTL lesions to provide richly detailed episodes during the simulation of personal past and future events is not due to a narrative deficit, being them able to describe the ongoing (perceptual) reality or events depicted in pictures, but truly mediated by a paucity of perceptual and contextual episodic details (Race, Keane, & Verfaellie, 2011; Race, Keane, & Verfaellie, 2013; Kurczek et al., 2015; St-Laurent, Moscovitch, & McAndrews, 2016). Therefore, MTLs and, specifically, the hippocampus, are a necessary underpinning of both episodic memory and episodic future thinking (reviewed in McCormick, Ciaramelli, De Luca, & Maguire, 2018).

MTLs are not the only structure found active during past and future simulation by neuroimaging studies, and, in the last decade, a growing number of neuropsychological studies have begun to investigate the contribution to episodic memory and episodic future thinking of other areas within the default mode network, mainly frontal and parietal regions. One the earliest neuropsychological studies of patients with frontal lesions is the famous case of Phineas Gage, who reported a huge damage of the prefrontal cortex, including its ventromedial portion (vmPFC), due to a work accident; the lesion caused him striking behavioural changes, mainly related to decision making and emotional regulation ability, with apparently no effects on memory (Harlow, 1848). Curiously, Harlow reported that Gage might have suffered from confabulation. Later, it has been found that bilateral prefrontal lesions, which include the vmPFC, frequently result in serious difficulties at recollecting autobiographical memories (Della Sala, Laiacona, Spinnler, & Trivelli, 1993; Kopelman, Stanhope, & Kingsley, 1999). Importantly, while patients with MTLs and hippocampus lesions tend to remember past events with less episodic specificity and fewer details (Rosenbaum, Gilboa, Levine, Winocur, & Moscovitch, 2009; Race, Keane, & Verfaellie, 2011; Kurczek et al., 2015), patients with prefrontal lesions tend to retrieve fewer autobiographical memories than healthy controls, and this deficit is correlated to poor executive functions (Della Sala et al., 1993). Moreover, they tend to displace their memories along a time-line more than MTL and hippocampal patients do (Tranel & Jones, 2006). This memory profile led to infer that a damage to the vmPFC may alter retrieval strategies (Moscovitch, 1995; Moscovitch & Melo, 1997) or knowledge structures, called schema, involved in the organization of episodic memories (Gilboa and Marlatte, 2017). The episodic memory deficit in prefrontal patients is extended to the future domain. In fact, vmPFC patients are impaired at imagining personal recent and remote future events, providing fewer episodic and contextual details than matched controls (Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016; Bertossi, Tesini, Cappelli, & Ciaramelli, 2016). Importantly, unlike MTL patients (Race, Keane, & Verfaellie, 2013), vmPFC patients have also poor narrative skills, providing fewer episodic details also during the description of pictures; however, controlling

for performance in the description condition do not eliminate their deficit in the simulation of future events (Bertossi, Candela, De Luca, & Ciaramelli, 2017). Therefore, the prefrontal cortex, and more specifically, the vmPFC, have a necessary role in both episodic memory and episodic future thinking (reviewed in McCormick, Ciaramelli, De Luca, & Maguire, 2018).

Furthermore, a striking dissociation has been observed between spared and impaired autobiographical memory retrieval in vmPFC and MTL patients. vmPFC patients have been found impaired at recalling autobiographical memories of extended events lasting from hours to 1 day (Bertossi, Tesini, Cappelli, & Ciaramelli, 2016). However, in a study requiring to describe only selected moments extracted from extended past or future events, vmPFC patients performed normally (Kurczek et al., 2015). By contrast, MTL patients have been found impaired at describing even single moments extracted from extended past events (Kurczek et al., 2015). Although this dissociation needs to be taken with caution because it is gathered from two different studies, it suggests that patients with MTL damage may find difficult to evoke even one scene in their mind's eye, while those with vmPFC damage might be impaired in visualizing how extended events unfold.

It is worth noting that the posterior parietal lobe (PPC) also contributes to episodic memory and episodic future thinking, although its role has been less explored than that of MTLs and vmPFC. Early neuropsychological investigations of patients with PPC lesions considered the memory impairment exclusively in terms of impaired spatial imagery (Critchley, 1953), and, indeed, the concomitant presence in these patients of perceptual and spatial deficits, like hemispatial neglect, has limited a precise examination of the episodic memory domain (reviewed in Berryhill, 2012). However, more recently, single cases of damage to right PPC, patient D.H. (Hunkin, Parkin, Bradley, & Burdon-Cooper, 1995), and left PPC, patient S.M. (Davidson et al., 2008), have revealed an impaired autobiographical memory and recollection in these patients, along with a lack of sense of re-experience of the event itself. A poor subjective re-experience of the contextual elements of the recollected memories has, in fact, been associated to the PPC lesions (Drowos,

Berryhill, André, & Olson, 2010; Ciaramelli et al., 2017). This autobiographical memory impairment has been further studied in two patients with PPC damage, who reported impoverished memories during free recall of personal past events, but normally detailed memories following specific probe questions, showing a dissociation between spontaneous and guided autobiographical memory retrieval (Berryhill, Phuong, Picasso, Cabeza, & Olson, 2007). Again, the episodic memory impairment was mirrored by a future thinking deficit, since patients with bilateral PPC lesions have been found unable to envision richly detailed future events, and their imagined future scenarios specifically lacked of spatial integration (Berryhill, Picasso, Arnold, Drowos, & Olson, 2010). Therefore, the posterior parietal cortex, along with MTLs and vmPFC, seems to have a necessary role in both episodic memory and episodic future thinking.

As the commonalities between episodic memory and episodic future thinking are significant at both cognitive and neural level, different theoretical accounts have been proposed to explain this striking overlap, as discussed in the next paragraph.

1.3 Hypotheses on the component processes of episodic memory, future thinking, and other forms of mental event construction

The similarities between episodic memory and episodic future thinking reviewed in the previous section gave rise to a number of interpretations of the possible underlying process common to both domains. According to the *constructive episodic simulation hypothesis* (Schacter & Addis, 2007a; Schacter & Addis, 2007b; Schacter, Addis, & Buckner, 2007), past and future events draw on similar information and rely on similar underlying processes, and episodic memory has the critical function of supporting future simulation by allowing individuals to retrieve and flexibly recombine elements of past episodes into novel representations of events that might occur in the future. Based on this view, the retrieval of information from episodic memory is not seen as a mere reproduction of past experiences, but as an active re-construction process of binding together bits of information, extremely adaptive in order to simulate future scenarios (Schacter & Addis, 2007a;

Schacter & Addis, 2007b). The re-constructive nature of episodic memory can explain why it is susceptible to memory errors, like source misattribution and false recognition, which are the by-product of wrongly combining elements of distinct past experiences. This approach does not emphasize much temporal aspects such as mental time travel (Suddendorf and Corballis, 1997, 2007; Tulving, 2002), but focuses more on processes involved in linking together distinct elements of an episode, like relational processing related to hippocampal function (Eichenbaum & Cohen, 2001), that may contribute to the construction of simulated events.

An alternative account suggests that remembering personal past experiences and thinking about the future share the common process of *self-projection,* the act of mentally project the self into an alternative situation, be this a past or future event (Buckner & Carroll, 2007). Indeed, there is evidence showing that different ways of decoupling from the present, like remembering the past, envisioning the future, conceiving the viewpoint of others (theory of mind) and some forms of spatial navigation, all activate the same core brain network of frontal, temporal and parietal regions overlapping with the default mode network (Raichle et al., 2001). In line with this view, it has been suggested that this core brain network or regions can be seen as the fundamental correlate of any form of mental detachment from the immediate environment to internal modes of cognition (Buckner & Carroll, 2007). Therefore, according to this view, mental time travel is just one form of disengaging from the immediate environment (Buckner & Carroll, 2007).

In sharp contrast with the idea of the self-projection into alternative perspectives (Buckner & Carroll, 2007), Maguire and colleagues have argued that it is the process of *scene construction*, the act of mentally generating and maintaining a complex and coherent scene (Hassabis & Maguire, 2007), that links together episodic memory and episodic future thinking. Indeed, both these abilities are invariably based on the construction and visualization of multiple spatial scenes, conceived as the backbones of past, future and even atemporal experiences (Hassabis & Maguire, 2007). Importantly, these authors found evidence that even the imagination of fictitious experiences, not explicitly connected to either the self or to a subjective sense of time, is reliant on the same brain

network involved in the recollection of past episodes and the imagination of future events (Hassabis, Kumaran, & Maguire, 2007). Therefore, the act of mentally generating and maintaining a complex and coherent scene, fulfilled by the retrieval and integration of perceptual, semantic and contextual information integrated in a coherent spatial context, is seen as the core process underlying episodic memory and episodic future thinking, as well as many other cognitive abilities involving the visualization of scenes in one's own mind eye (e.g. navigation, vivid dreaming). This hypothesis does not consider the concept of time as of primary importance in explaining the common activity related to different forms of event simulation, and the temporal direction (past or future) of an event is seen just as the result of a content or goal difference, rather than a change in the basic processes involved (Hassabis & Maguire, 2007; Hassabis & Maguire, 2009). Instead, much emphasis is placed on constructive processes needed to bind together disparate types of information into a coherent scene (Hassabis & Maguire, 2007). Since that the subsequent experimental investigations reported in this thesis are aimed to show the contribution of specific cortical structures to the process of scene construction, this theory will be explained in more detail in the next section.

2. Scene construction

The scene construction theory (Hassabis & Maguire, 2007) has been proposed to explain the common cognitive and neural bases of episodic memory and episodic future thinking, as well as other mental capabilities that involve the generation, visualization and maintenance of complex and coherent spatial scenes. This constructive process stems from the reactivation, retrieval and integration of relevant semantic, contextual and sensory information, stored in their modality specific cortical areas (Wheeler, Petersen, & Buckner, 2000), and the product of this process is a coherent spatial context (Hassabis, Kumaran, & Maguire, 2007), which can be manipulated and visualized. Complex and coherent spatial scenes can be considered the backbones of any simulated experience, because when we remember personal past episodes, we envision events that might

happen in the future or fictitious scenarios without any temporal constraints, when we mentally navigate in different environments, and even when we daydream, we, first of all, automatically create and see scenes in our own's mind eye. A scene is "a naturalistic three-dimensional space which one could potentially step into and operate within, viewed from a first person perspective and populated by objects" (Dalton & Maguire, 2017). In this respect, the construction of a scene differs from "simple" visual imagery, such as that for single objects (Kosslyn, Ganis, & Thompson, 2001), and could, instead, be considered a form of "associative construction", because it requires not only visual imagery, but also the flexible association, binding and integration of different multimodal elements to (re)create an event as a whole (Hassabis & Maguire, 2009).

Considering how much important and pervasive the act of constructing scenes is for the human cognition, it seems of particular interest to understand its cognitive mechanisms and neural underpinnings. In the next paragraphs, the neural circuits and structures deputed to the scene construction process will be addressed, along with their cognitive role.

2.1 Neural bases of scene construction

Evidence from neuroimaging

The main evidence of a common underlying scene construction process to episodic memory and episodic future thinking comes from a fMRI study showing that the imagination of fictitious, atemporal scenarios (e.g., commonplace, ordinary settings, like "Imagine you are lying on a sandy beach in a tropical bay"), not requiring to travel in the subjective time and not strictly related to the self, activates the same network of regions involved in the (re)construction of past and future experiences, and comprising hippocampus, parahippocampal gyrus, retrospenial cortex, posterior parietal cortex, and medial prefrontal cortex (Hassabis, Kumaran, & Maguire, 2007). A conjunction analysis revealed, in particular, that a subset of brain regions is activated by both the recall of real experiences and the construction of novel, fictitious experiences. This network of brain regions could be referred to as the "construction system" (Hassabis & Maguire, 2009), because presumably

involved in scene or event generation, the primary process that all those cognitive functions share, and includes the hippocampus bilaterally, parahippocampal gyrus, retrosplenial cortex, posterior parietal cortex, middle temporal cortices and medial prefrontal cortex (Hassabis, Kumaran, & Maguire, 2007). Of note, the construction network does not overlap with the network of areas involved in object representations and manipulations, namely lateral occipital complex and intraparietal sulcus bilaterally (Sugiura, Shah, Zilles, & Fink, 2005), suggesting that the construction of complex scenes is a process distinct from the "simple" visual imagery of single objects and it requires a segregate and more extended neural network. Furthermore, two areas within the construction system, hippocampus and parahippocampal cortex, have been found involved even in the initial automatic extrapolation of single scenes beyond their physical borders after a brief observation of scene pictures, and this effect seems to be driven by the hippocampus, which exerts top-down influence on parahippocampal cortex and early visual cortex (Chadwick, Mullally, & Maguire, 2013). Hippocampus and parahippocampal cortex are also active during the detection of spatial incoherency and coherency, respectively, while observing spatial impossibilities in Escher-like scenes, suggesting a role of these regions in binding distinct features into coherent representations (Douglas et al., 2016).

Evidence from neuropsychology

Evidence coming from neuropsychological studies has confirmed that the key nodes within the construction system are necessarily involved in the construction of scenes. A first study revealed that amnesic patients, with lesions restricted to the hippocampus, unable to vividly remember their past and envision their future, were also incapable to imagine fictitious scenarios without any requirement for mental time travel or self-projection, and that their simulated experience was lacking in spatial coherence and mainly consisted of fragments of images not bound to an holistic representation of the environmental context (Hassabis, Kumaran, Vann, & Maguire, 2007a). Similarly, amnesic patients with scene construction deficit are unable to automatically extrapolate beyond scene boundaries after a brief observation of scene pictures, showing an attenuated

boundary extension effect (Mullally, Intraub, & Maguire, 2012), and are impaired at detecting constructive violations during the observation of spatial impossibilities in Escher-like scenes (McCormick, Rosenthal, Miller, & Maguire, 2017) (see Chapter 3 for more details).

Performance of patients with damage to the vmPFC highly mimics that of hippocampal patients. vmPFC patients, who show deficit at simulating personal past and future events, are also impaired at imagining fictitious, atemporal scenarios (Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016), even if differences also emerge in the scene construction performance of patients with vmPFC vs. hippocampal damage, as we will show in Chapter 3. Finally, patients with damage to the posterior parietal cortex, who show deficit at simulating personal past and future events, are also impaired at imagining fictitious scenarios; in the "constructed experiences task" (Hassabis, Kumaran, & Maguire, 2007), indeed, they simulate atemporal experiences with fewer entities presence, thoughts/emotions/actions, sensory descriptions and spatial references, and poorer in spatial coherence than their matched controls (Berryhill, Picasso, Arnold, Drowos, & Olson, 2010). Further evidence found that patients with parietal damage due to posterior cortical atrophy are incapable at constructing fictitious scenarios, and their simulated experiences are specifically impoverished and spatially fragmented, suggesting that visual imagery has a fundamental role in the construction of mental scenes (Ramanan et al., 2018). Therefore, key nodes of the construction system, namely hippocampus, vmPFC and posterior parietal cortex, are necessary to generate, visualize and maintain single and multiple complex scenes. Their peculiarities will be further explained in the next paragraph.

2.2 Role of key neural nodes of the construction system

Within the construction network, different regions seem to contribute in distinct ways to the generation of complex scenes. One key node of this network, as explained, is the posterior parietal lobe (PPC). The PPC has strong connections with visual areas (Colby, Gattass, Olson, & Gross, 1988; Blatt, Andersen, & Stoner, 1990), being part of the occipito-parietal dorsal stream involved in

visuospatial processing (Mishkin, Ungerleider, & Macko, 1983; Goodale & Milner, 1992; Milner & Goodale, 2008). In the dorsal PPC, the precuneus is directly connected with medial (RSC and PCC) and lateral (IPL, SPL) portions of the parietal lobe (Leichnetz, 2001), areas all implicated in visuospatial processing (Sakata & Kusunoki, 1992; Vann, Aggleton, & Maguire, 2009; Auger & Maguire, 2018). Importantly, the precuneus is not directly connected with primary sensory regions (Leichnetz, 2001), leading to assume that its activity influences an extensive network of cortical and subcortical structures deputed to elaborate highly integrated and associative information, rather than directly processing external stimuli (Cavanna & Trimble, 2006). Indeed, the inferior precuneus is active during the imagination of complex scenes in three-dimensional space, without any visual cue (Dalton, Zeidman, McCormick, & Maguire, 2018).

In the ventral PPC, the IPL, along with PCC and RSC, areas implicated in visuospatial processing and contextual associations (Sakata & Kusunoki, 1992; Bar, Aminoff, & Schacter, 2008; Vann, Aggleton, & Maguire, 2009; Mullally & Maguire, 2011; Auger, Zeidman, & Maguire, 2015), sends direct projections to the pre/parasubiculum, the medial-most portion of the hippocampus, giving it privileged access to this high-order and integrated visuospatial information (Kravitz, Saleem, Baker, & Mishkin, 2011). For this reason, the pre/parasubiculum is considered the hippocampal hub of a broader scene processing network (Dalton & Maguire, 2017; Dalton, Zeidman, McCormick, & Maguire, 2018).

By virtue of these connections with high-order visuospatial processing areas and of the presence of cell populations involved in spatial processing (i.e., place, grid and border cells, O'Keefe & Dostrovsky, 1971; Fyhn, Molden, Witter, Moser, & Moser, 2004; Boccara et al., 2010), the hippocampus, mainly in its anterior portion (Zeidman & Maguire, 2016; Dalton & Maguire, 2017; Dalton, Zeidman, McCormick, & Maguire, 2018), is deemed to play a crucial role in the construction system, and be responsible of the building of a visuospatial scaffold of mental scenes (Hassabis, Kumaran, & Maguire, 2007; Hassabis, Kumaran, Vann, & Maguire, 2007; Andrews-hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Mullally, Intraub, & Maguire, 2012;

McCormick, Ciaramelli, De Luca, & Maguire, 2018). In particular, the anterior portion of the hippocampus is deemed critical to engage in "offline" processes, as the construction of a spatially coherent scene representation during imagination and recall, but it also active in "online" processes, as the representation of perceived scenes, whereas the posterior hippocampus is more exclusively involved in "online" processes of visual perception, although it has been suggested that differences along the hippocampal axis can be understood as a gradient in level of detail, from coarse representations in anterior hippocampus to fine detail in the posterior (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; see Zeidman & Maguire, 2016 for a review).

The anterior hippocampus is known to be particularly well connected with the ventromedial portion of PFC (vmPFC; Adnan et al., 2015; Catani et al., 2012; Catani, Dell'Acqua, & Thiebaut de Schotten, 2013), and, indeed, many similarities in the functional properties of these two regions of the construction system have been found, which we recently reviewed (McCormick, Ciaramelli, De Luca, & Maguire, 2018). Our review, however, helped us realize that even though the vmPFC and hippocampus are both necessary to construct complex mental scenes in a variety of tasks, these regions seem to contribute differently and in a complementary way to the construction process, and this is apparent in several domains. As anticipated, vmPFC patients fail to generate as many autobiographical event memories as healthy controls (Della Sala et al., 1993; Kopelman, Stanhope, & Kingsley, 1999), and they construct both past and future events poor in episodic detail (Bertossi, Tesini, Cappelli, & Ciaramelli, 2016; Bertossi, Candela, De Luca, & Ciaramelli, 2017), but they are capable to describe in detail single snapshot scenes taken from their memories and imagined events (Kurczek et al., 2015), whereas, hippocampal patients are incapable to construct in detail even single snapshot scenes from these memories and imagined events (Kurczek et al., 2015). During the construction of fictitious scenarios, vmPFC patients simulate experiences generally lacking of content and spatial coherence (Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016), whereas hippocampal patients simulate experiences specifically lacking of spatial coherence (Hassabis, Kumaran, Vann, & Maguire, 2007). Differences are also apparent during mind-wandering, when

individuals shift attention away from the external environment toward inner self-generated thoughts (Smallwood & Schooler, 2015). vmPFC patients seem to be unable to initiate internal reflections, and their off-task thoughts are more related to the present than to the future (Bertossi & Ciaramelli, 2016), whereas hippocampal patients seem able to initiate these internal reflections, but their thoughts are devoid of vivid visual representations of scenes (McCormick, Rosenthal, Miller, & Maguire, 2018). Lastly, difficulties in scene construction can also affect spatial navigation. The amnesic patient K.C. was unable to produce a detailed description of his neighborhood, despite having lived there for most of his life (Rosenbaum et al., 2000; Rosenbaum, Gao, Richards, Black, & Moscovitch, 2005); and a hippocampal patient, who was a former London taxi driver, was unable to reach a goal location if the route required to take small roads, though he could compensate using main artery (overlearned) A-routes (Maguire, Nannery, & Spiers, 2006). The only one vmPFC patient examined in an ecological navigation task, showed difficulties in wayfinding in his home town. Notably, he proved to have intact knowledge for landmarks and routes, but to lose his goal destination while navigating, being attracted by familiar landmarks and previously attended locations along the route (Ciaramelli, 2008). These findings suggest that hippocampal damage might impair the ability to visualize a mental scene necessary to navigate the environment, whereas a vmPFC damage may impair the ability to initiate mental reminders at critical points in the route planning.

All these findings converge on the idea the vmPFC and hippocampus co-operate in a hierarchical manner during the construction of mental complex scenes, where the hippocampus plays a subordinate role. In particular, it has been suggested (McCormick, Ciaramelli, De Luca, & Maguire, 2018) that vmPFC might act as a supervisor that initiates endogenous processes like scene construction. According to this view, the vmPFC would coordinate the collection of relevant elements from neocortical areas and then would funnel them into the hippocampus to build the spatial structure of the scene. Then the vmPFC would engage in iterative re-initiation via feedback

loops with neocortex and hippocampus to facilitate the flow of multiple scenes, to form the coherent unfolding of an extended mental event (McCormick, Ciaramelli, et al., 2018).

This proposal finds support from data showing that during the formation of new memories, electrophysiological power changes can be seen almost immediately after stimulus onset in the vmPFC and remain there until the end of the stimulus, whereas power changes in the hippocampus occur much later, around 500-2000 ms after stimulus onset (Sederberg et al., 2007). Furthermore, vmPFC influences match-mismatch novelty responses in the hippocampus (Garrido, Barnes, Kumaran, Maguire, & Dolan, 2015), and drives activity in the hippocampus during the imagination of novel scenes (Barry, Barnes, Clark, & Maguire, preprint). The vmPFC is also involved in the storage and retrieval of semantic knowledge (Cabeza & Nyberg, 2000; Assaf et al., 2006; Binder, Desai, Graves, & Conant, 2009) and in the instantiation of "schemas", superordinate knowledge structures that reflect abstracted commonalities across multiple experiences (Ghosh & Gilboa, 2014; Gilboa & Marlatte, 2017), around which imagined events can be constructed. In contrast, the involvement of the hippocampus seems to be specifically driven by the construction of a spatially coherent mental scene into which details can be bound to be re- or pre-experienced (Hassabis, Kumaran, Vann, & Maguire, 2007; Mullally et al., 2012; McCormick, Rosenthal, Miller, & Maguire, 2017).

Since vmPFC and hippocampus assume such a crucial and well characterized role in the scene construction process, the remaining part of this section will be focussed on specifying in detail their anatomical structure and connectivity and their different contribution to scene construction.

2.2.1 Anatomy and connectivity of the hippocampus and vmPFC

The hippocampus is situated in the medial temporal lobe (MTL) of each hemisphere and has a distinct, curved shape, whose appearance resembles that of a seahorse (Amaral & Witter, 1989). It consists of two layers rolled up inside each other. The first of these, the dentate gyrus, is wrapped

around the second layer, forming a semicircle in cross-sectional views. The second layer consists of a series of Cornu Ammonis (CA) areas that define the subfields of the hippocampus, namely, CA1, CA2, CA3, and CA4 (Sloviter & Lømo, 2012). Other parts of the hippocampus include the subiculum, presubiculum, parasubiculum, prosubiculum and the uncus. Because of limitations in the spatial resolution of most neuroimaging techniques, it is common to refer to the "CA2/3", "pre/parasubiculum" and "prosubiculum/CA1" as unitary subfields (Dalton, Zeidman, Barry, Williams, & Maguire, 2017; Dalton & Maguire, 2017). The hippocampus and the adjacent entorhinal, perirhinal and parahippocampal cortices constitute the MTL. In the MTL system, the entorhinal cortex is the main gateway between most neocortical brain regions and the hippocampus.

The vmPFC is a part of the prefrontal cortex in mammals, comprising its bottom (ventral) and central (medial) portions (Ongur, Ferry, & Price, 2003; Mackey & Petrides, 2010). There are no clear anatomical landmarks for this area, thence it is generally defined as the subgenual region, beneath the genu of the corpus callosum. The vmPFC includes Brodmann areas 25 and 32 (the subgenual portion), as well as 10 (the most rostral part), 11, 12 and 47 (the orbital part). It is surrounded by other parts of the prefrontal cortex that are commonly described based on their locations as ventrolateral, dorsomedial and dorsolateral PFC, and all these portions are connected via short frontal pathways (Catani et al., 2012).

In humans, the hippocampus and vmPFC are anatomically connected via three main reciprocal connections - the uncinate fasciculus, the fornix and the cingulum bundle (Concha, Gross, & Beaulieu, 2005; Malykhin, Concha, Seres, Beaulieu, & Coupland, 2008; Catani, Dell'Acqua, & Thiebaut de Schotten, 2013). The uncinate fasciculus connects the anterior part of the temporal lobe, including hippocampus, to the ventral and polar areas of the frontal cortex. Fornix fibers arise mainly from the hippocampus and entorhinal cortex and connect the two hippocampi to each other and to the mammillary bodies. Also, fornix fibers reach the most posterior part of the vmPFC going forward beneath the corpus callosum. The cingulum bundle is a large pathway containing fibers of different lengths, with the longest fibers connecting the anterior

hippocampus and parahippocampal gyrus to the vmPFC. These fibers run above the corpus callosum, with shorter fibers joining and leaving the cingulum bundle along its length. A fourth indirect pathway connects the vmPFC to the hippocampus via the mammillothalamic tract and anterior thalamic projections.

The anterior hippocampus has particularly strong connections with the vmPFC, as confirmed by findings from diffusion-weighted imaging and functional connectivity of resting state fMRI data (Andrews-hanna et al., 2010; Adnan et al., 2015). Lesions to either the hippocampus or vmPFC likely impact their connectivity and, as these disconnections are mostly messy (e.g., following a ruptured aneurysm), they can be partial or total, and might only affect one, two or all three of the main pathways connecting these two regions (Liao et al., 2011; Hepdurgun et al., 2016), making problematic to isolate the independent functions of both regions. Furthermore, anatomical routes connecting the hippocampus and vmPFC to other parts of the brain can also be disrupted. These other brain areas (e.g. the thalamus) are potentially transfer stations, serving as indirect anatomical connections between hippocampus and vmPFC (Catani et al., 2013).

2.2.2 Connectivity between the hippocampus and other regions within the construction system

The pre/parasubiculum, in the anterior medial portion of the hippocampus (Zeidman & Maguire, 2016; Hodgetts et al., 2017), is a primary hippocampal target of the parieto-medial temporal pathway (Kravitz, Saleem, Baker, & Mishkin, 2011), which stems from the caudal portion of the inferior parietal lobule, part of the dorsal occipito-parietal stream. The inferior parietal lobule sends direct projections to the posterior cingulate cortex, retrosplenial cortex and parahippocampal cortex, and, in turn, inferior parietal lobule, posterior cingulate cortex and retrosplenial cortex each send direct projections to pre/parasubiculum and prosubiculum/CA1 (Kravitz et al., 2011). Importantly, the occipito-parietal stream is deemed to integrate information from both foveal and peripheral visual fields equally (Boussaoud, Ungerleider, & Desimone, 1990; Kravitz, Saleem,

Baker, Ungerleider, & Mishkin, 2013); therefore, the downstream parieto-medial temporal pathway sends integrated visual input to target regions, such as posterior cingulate cortex and retrosplenial cortex, which then in turn send integrated visual information to the pre/parasubiculum, which has, indeed, privileged access to holistic representations of the environment (Dalton & Maguire, 2017).

2.2.3 Connectivity between the vmPFC and other regions within the construction system

The frontal pole has two main intralobar tracts: the fronto-orbitopolar tract, which gets through the ventral aspect of the frontal lobe and connects the posterior orbital gyrus to the anterior orbital gyrus and ventromedial region of the frontal pole; and the fronto-marginal tract, which runs beneath the fronto-marginal sulcus and connects medial and lateral regions of the frontopolar cortex (Catani et al., 2012). As for the fronto-orbital part of the frontal pole, different patterns of connectivity are distinguishable in its anterior and posterior portions. The anterior orbitofrontal cortex receives sensorial information (e.g., visual and auditory inputs) from posterior occipital and temporal cortex through the inferior fronto-occipital and uncinate fasciculus (Price, 2007; Thiebaut de Schotten et al., 2011; Thiebaut de Schotten, Dell'Acqua, Valabregue, & Catani, 2012), whereas, the posterior orbital cortex receives sensorial (e.g., olfactory and gustatory inputs) and emotional information from the limbic regions (i.e., amygdala, hippocampus, nucleus basalis of Meynert, olfactory cortex and insula) (Price, 2007). Due to these diversified connections, the fronto-orbital pole can be considered a transmodal network for binding memories and emotions with olfactory, taste, visual and auditory information (Catani et al., 2012). Importantly, the visual information conveyed by the inferior fronto-occipital fasciculus may have a potential role in the generation of a basic template during the construction of visual complex scenes. Indeed, an increased functional connectivity between vmPFC and object-sensitive lateral occipital cortex (LOC) has been found during the visual search of specific objects within a complex natural scene (Pantazatos, Yanagihara, Zhang, Meitzler, & Hirsch, 2012).

As shown, the intricate pattern of connectivity between the hippocampus and vmPFC and between them and other regions within the construction system, put these two nodes in the ideal position to exercise a vital role in the construction process of complex mental scenes. In the following section, we will come back to one expression of event construction, the episodic future thinking, and focus on its adaptive functions and role in decision making.

3. Functions of episodic future thinking

As explained in the first section, episodic future thinking has been conceived as the act of mentally project oneself into the future, to pre-experience situations never experienced before (Atance & O'Neill, 2001; Gilbert & Wilson, 2007). The simulation of future scenarios is a pervasive mental activity, so much so that individuals spontaneously engage in future event representations without any preceding search attempt (Berntsen & Jacobsen, 2008), experiencing – it has been noted – up to one future oriented thought every 16 minutes during the day (D'Argembeau, Renaud, & Van Der Linden, 2011), and spending much more time thinking about their future than their past (Jason, Schade, Louise, Reichler, & Brickman, 1989). The high frequency of future-oriented thoughts must say something about their role in human cognition.

It has been proposed, indeed, that simulations, in particular, episodic future thoughts, are highly adaptive and subserve a range of cognitive functions (see Schacter et al., 2012; Schacter, Benoit, & Szpunar, 2017 for reviews). EFT can enhance prospective memory, contributing to the effectiveness of implementation intentions, because imagining to perform an upcoming intention makes it more likely that this intention will be actually conducted (Papies, Aarts, & de Vries, 2009; Neroni, Gamboz, & Brandimonte, 2014). It also enhances retrospective memory, because future-oriented encoding produces superior recall of word-list than past-oriented encoding (Klein, Robertson, & Delton, 2010; Klein, Robertson, & Delton, 2011). EFT has been found to improve psychological well-being and emotional regulation (Taylor, Pham, Rivkin, & Armor, 1998; Brown, Macleod, Tata, & Goddard, 2002; Macleod, 2016). In particular, an episodic specificity induction,

namely, a brief training in recollecting details of past experiences (Madore & Schacter, 2014), carried out before simulating possible solutions to personally worrisome future events, makes individuals better able to reappraise the event and improves the subjective well-being (Jing, Madore, & Schacter, 2017).

The positive effect of EFT on emotional regulation may be due to the positivity bias that frequently characterizes future thinking (Sharot, 2011; Barsics, Van der Linden, & D'Argembeau, 2015) and the vivid recollection of (rosy) simulated future scenarios (Szpunar, Addis, & Schacter, 2012). This may be related to the fact that positive future thoughts contain more visual images than negative thoughts (D'Argembeau & Van der Linden, 2004; D'Argembeau, Renaud, & Van Der Linden, 2011), and the visualization of desired future events may aid in goal attainment, by enhancing expectation of success, boosting motivation and helping to set concrete plans and problem-solving activities (Taylor, Pham, Rivkin, & Armor, 1998; Conway, Meares, & Standart, 2004). EFT also benefits goal-directed cognition, supporting planning and problem solving, because it provides access to all the specific information necessary to generate problem solutions and it has a causal structure similar to that of an actual situation (Taylor, Pham, Rivkin, & Armor, 1998; Sheldon, McAndrews, & Moscovitch, 2011); in turn, thinking about personal goals facilitate the access to personal episodic details, improving EFT (D'Argembeau & Mathy, 2011). The relationship between EFT and goal-directed cognition calls into question the act of making choices about the future; this will be explained in the next paragraph.

3.1 Episodic future thinking and future-based decision-making

In the context of goal-directed cognition, EFT can also have beneficial consequences on decisions about the future, such as intertemporal choices, when individuals are faced with decisions regarding two reward options that differ in magnitude and delay until delivery, and tend to show the phenomenon of delay discounting, devaluing larger but more distant rewards and preferring smaller but more proximal rewards (Green & Myerson, 2004). Delay discounting is related to impulsivity

(Green, Myerson, Lichtman, Rosen, & Fry, 1996; Green & Myerson, 2004), and it has been suggested that the simulation of the future may help individuals to represent distant future rewards more vividly, allowing individuals to show less impulsive and more farsighted decisions, thus reducing delay discounting (Boyer, 2008). Indeed, several attempts to link EFT to decision-making have confirmed Boyer's insight and proved the ability of future simulation to reduce impulsive decisions. Researchers have modified the classic temporal discounting paradigm and found that when people imagine specific future episodes before choosing between the two rewards options, they are more likely to prefer rewards that produce greater long-term payoffs, thus diminishing the normal impulsive tendency to devalue delayed rewards and making more patient choices (Peters & Büchel, 2010; Benoit, Gilbert, & Burgess, 2011; O'Donnell, Daniel, & Epstein, 2017). Importantly, the strength of the episodic effect on intertemporal choices is mediated by the degree of spontaneous episodic imagery during decision making and is associated to increased functional coupling between medial prefrontal regions and hippocampus (Peters & Büchel, 2010; Benoit, Gilbert, & Burgess, 2011). Since both these regions are involved in reward processing (McClure et al., 2004; Kable & Glimcher, 2007) and future thinking (Addis, Wong, & Schacter, 2007; Botzung, Denkova, & Manning, 2008), and since both prefrontal regions and hippocampus are necessary to construct scenes (Hassabis, Kumaran, Vann, & Maguire, 2007; Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016), these regions may have contributed to modulate decision making through their role in the vivid representations of future events, allowing the actual projection of the self into simulated events (Peters & Büchel, 2010).

This important finding on healthy people has been then applied to populations of individuals suffering from different forms of impulsivity and maladaptive behaviours, like addicts or adolescents. People suffering from different forms of addiction, like alcohol (Snider, LaConte, & Bickel, 2016), food (Daniel et al., 2013; O'Neill, Daniel, & Epstein, 2016) or drugs (Dennhardt et al., 2015; Stein et al., 2016) abuse, or young healthy people, like adolescents (Bromberg, Lobatcheva, & Peters, 2017), have shown a reduction of delay discounting following the episodic

simulation of future scenarios associated to future rewards. This high effectiveness of episodic future thinking in reducing impulsive behaviours gave rise to hopes about possible clinical applications of EFT and to interesting questions about the underlying mechanisms of the EFT-induced impulsivity reduction.

It has been suggested that the episodic simulation of the future may act as a brake on impulsiveness or a boost on patience during decision making process by triggering emotional circuitry that reflect the emotional impact of the hypothetical future situations, thus serving as an immediate reward, but also as a representation of the future scenarios, leading to reconsider more distant options and to reduce their devaluation (Boyer, 2008). This positive effect of episodic simulation on decision making may be related to the fact that imagining episodic details and specifics of a distant future scenario, confers to it more concrete and idiosyncratic features, making the distant future scenario closer and reducing its psychological distance from oneself' direct experience. This is a crucial concept of the "construal level theory" (Trope & Liberman, 2003; Troper & Liberman, 2010; Liberman & Trope, 2014), which posits that events that extend beyond the "here and now", like future events, require individuals to construct mental representations of them to be conceived. Thus, individuals engage in high-level construal to represent distant future events, when they can only extract their abstract and essential features; whereas, they use low-level construal to represent near future events, when their specific details are available and can be combined to create concrete and idiosyncratic representations of the event itself (Trope & Liberman, 2003; Troper & Liberman, 2010; Liberman & Trope, 2014). This latter low-level construal process seems to correspond to what episodic simulation does during future-based decision making, rendering distant future scenarios closer, more concrete, more accessible and, hence, more valuable, leading to an increased self-control and more patient choices (but see Fujita et al., 2006). The effect of episodic simulation on future-based decision making will be further explored in the last chapter of this thesis, in a population of patients, with damage to the vmPFC, known to be impaired in episodic future thinking (Bertossi, Aleo et al., 2016; Bertossi, Tesini et al.,

2016) and showing steep temporal discounting in intertemporal choice (Sellitto, Ciaramelli, & di Pellegrino, 2010). In the last chapter, vmPFC patients will be compared with patients with damage to the MTLs, similarly impaired in episodic future thinking (Race et al., 2011, Race et al., 2013), but showing normal temporal discounting rates (Kwan et al., 2012). The cognitive mechanisms mediating the effect of episodic simulation on temporal discounting of future rewards will be discussed, along with the different roles played by vmPFC and MTLs.

In the first chapter of this thesis, I will present a study highlighting the relation between episodic memory and episodic future thinking, investigating several forms of future thinking in a patient with focal retrograde amnesia. This study will help clarify the role played by episodic memory in episodic future thinking, and reveal the different contribution of episodic and semantic memory to the construction of future and fictitious experiences, as well as future-oriented decision making and cognition. In the second chapter, I will begin to explore the neural bases of mental (future) event construction, investigating episodic future thinking in patients with damage to the ventromedial prefrontal cortex (vmPFC). This study will confirm a deficit in episodic future thinking in vmPFC patients, and explore whether this deficit may relate, to some extent, to possible problems in working memory or narrative abilities in vmPFC patients. In the third chapter, I will further explore the role of vmPFC in event construction, this time narrowing the focus on the construction of single scenes, the core process of different forms of mental event construction. I will compare patients with damage to the vmPFC and to the hippocampus. This chapter comprises two experiments, the first investigating the implicit, automatic construction of single scenes allowing 'boundary extension', the second exploring constructive and semantic components of the scene construction process. These studies will provide important information about the different roles that vmPFC and hippocampus may play in the construction of scenes. Lastly, in the fourth chapter, I will come back to one specific form of mental event construction, episodic future thinking, and study its relation and possible contribution to decision making. I will investigate whether promoting

episodic future thinking in vmPFC patients reduces their temporal discounting rates, and suggest a role for vmPFC in guiding future-oriented choice.

Chapter 1.

Remembering the past to imagine the future.

In this chapter, I will examine the relationship between episodic memory and episodic future thinking, investigating several forms of future thinking in a patient with focal retrograde amnesia. This study will help clarify the role played by episodic memory in episodic future thinking and reveal the different contribution that episodic and semantic memory provide to the construction of future and fictitious experiences, as well as future-oriented decision-making and cognition.

Study 1. Episodic future thinking and future-based decision-making in a case of retrograde amnesia.

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(De Luca F, Benuzzi F, Bertossi E, Braghittoni D, di Pellegrino G, Ciaramelli E. 2018. 110:92-103. *Neuropsychologia*)

Introduction

Humans have the capability, and the inclination, to represent specific events that may happen to them in the future, also known as episodic future thinking (EFT; Atance and O'Neill, 2001; Szpunar, 2010). EFT is adaptive, because the simulation of future scenarios may inform decision-making (Boyer, 2008) and improve problem-solving (Taylor and Schneider, 1989; Sheldon et al., 2011). Moreover, EFT may oppose the tendency to prefer immediate over delayed gratification (Peters and Büchel, 2010; Benoit et al., 2011).

How do we construct future experiences and use them for decision-making? Research in cognitive neuroscience has highlighted a profound tie between EFT and episodic (autobiographical) remembering. Both capabilities are associated with activity in a core network of brain regions, including the ventromedial prefrontal cortex (vmPFC), the posterior cingulate cortex, the parietal

cortex, and the medial temporal lobes (MLTs) (Okuda et al., 2003; Addis et al., 2007; Szpunar et al., 2007; St. Jacques et al., 2017). This overlap may relate to the fact that imagining a novel event depends, in part, on retrieving information from episodic memories of similar experiences as source of details to create the novel experience (Buckner and Carroll, 2007; Hassabis and Maguire, 2007, 2009; Moscovitch, 2008; Schacter and Addis, 2007). In addition, both EFT and episodic remembering require constructive processes needed to assemble the individual elements composing the remembered/imagined event (i.e. episodic simulation; Schacter et al., 2012) and its spatial context (i.e scene construction, Hassabis & Maguire, 2007). Coherently, patients with lesions in key nodes of the core network, such as the MTLs (Hassabis, Kumaran, Vann, & Maguire, 2007; Rosenbaum, Gilboa, Levine, Winocur, & Moscovitch, 2009; Race et al., 2011), vmPFC (Bertossi, Aleo, et al., 2016; Bertossi, Tesini, et al., 2016) and the parietal cortex (Berryhill et al., 2007; Berryhill et al., 2010) are impaired in both episodic remembering and future thinking.

Other research has highlighted dissociations between episodic remembering and future thinking, which reveal additional component processes of EFT (Gilmore et al., 2017); for example, EFT is more heavily reliant on semantic memory than is episodic remembering, consistent with high levels of activity in the lateral temporal cortex for EFT (Addis et al., 2007). It has been proposed that during EFT semantic knowledge provides a "scaffold" from which relevant episodic details can be searched (Irish & Piguet, 2013). For example, knowledge about semantic life scripts (i.e. culturally expected events at particular time in the life span) (Thomsen & Berntsen, 2008) and personal goals drive construction of plausible future events (D'Argembeau & Mathy, 2011). Patients with semantic dementia, indeed, have impaired EFT in the face of preserved episodic remembering (Duval et al., 2012; Irish, Addis, Hodges, & Piguet, 2012; Irish, Addis, Hodges, & Piguet, 2012b). Not only semantic memory is necessary for EFT; it may be sufficient. Cooper et al. (2011) have found that children with developmental amnesia have impaired episodic remembering but are able to imagine novel experience (but see Kwan et al., 2010). The authors have argued that these patients may have developed semantically-based forms of event construction to circumvent

their episodic amnesia, consistent with their preserved semantic knowledge base (Cooper et al., 2011). The same pattern of results was noted in P01, a patient with amnesia acquired in adulthood (Hassabis, Kumaran, Vann, et al., 2007). P01 had retained semantic learning abilities and intact personal and general semantics (Maguire et al., 2010), and residual hippocampal tissue (Mullally et al., 2014), which may underlie his successful construction performance. EFT also loads on executive functions to a greater extent than does episodic remembering, because it requires the flexible recombination of details from multiple episodes into a novel event (Schacter et al., 2012). Indeed, patients with lesions in the lateral prefrontal cortex (Berryhill et al., 2010), or in the medial dorsal thalamus (Weiler et al., 2011), which is densely connected with prefrontal cortex, have impaired EFT in the face of preserved episodic remembering.

EFT is also dissociable from other ways of conceiving the future. First, although amnesic patients cannot imagine personal future experiences, they generally maintain the ability to imagine future public events or facts that might be true at a future time (Tulving, 1985; Klein et al., 2002; Cooper et al., 2011; Hurley et al., 2011; Race et al., 2011), unless they are required to generate specific details relating to those events (Race et al., 2013). Moreover, patients with amnesia typically understand the concept of time, can orient themselves with respect to their personal past and future (Arzy et al., 2009; Craver et al., 2014; Kwan et al., 2013), and have normal delay discounting of future rewards (Kwan et al., 2012, 2013), suggesting that EFT is just one of several mechanisms mediating future-oriented cognition and choice.

In the current study, we explore the relation between autobiographical remembering, EFT, and future-oriented decision-making in SG, a case of focal retrograde amnesia (FRA). FRA (Kapur, 1993, Evans et al., 1996; Carlesimo et al., 1998a, 1998b; Kopelman, 2000) also known as 'isolated retrograde amnesia' (Levine et al., 1998; Fast and Fujiwara, 2001), or 'pure retrograde amnesia' (De Renzi et al., 1997; Lucchelli and Spinnler, 2002) refers to a state of grossly impaired memory for information acquired prior the onset of brain damage contrasted with normal, or minimally impaired, learning of new information. FRA most commonly entails a profound loss of

autobiographical episodic memory, with relatively preserved (public, personal, and general) semantic knowledge, even though several cases of uniformly compromised episodic and semantic memory have been reported as well (see Wheeler and McMillan, 2001, for a review). FRA is most commonly precipitated by traumatic brain injury (Markowitsch et al., 1993; Hunkin et al., 1995; Kapur, 1999), herpes simplex encephalitis (O'Connor et al., 1992; Yoneda et al., 1994; Hokkanen et al., 1995), hypoxia (De Renzi and Lucchelli, 1993; Reed et al., 1999), and Korsakoff syndrome (Kopelman, 1989; Parkin et al., 1990), and is typically associated with multifocal lesions. FRA, however, may also characterize cases of memory loss in which psychological factors co-occur with a (minor) physical injury (Schacter et al., 1982; Dalla Barba et al., 1997; Stracciari et al., 2005), or functional deficits with no apparent organic or psychogenic cause (Ennio De Renzi et al., 1997).

As anticipated, one crucial feature of FRA is the severe loss of retrograde memory, combined with a largely preserved anterograde memory. Studying EFT and future-based decision making in a case of disproportionate retrograde amnesia will help explore further the relation between autobiographical memory and EFT, in a way that will complement extant studies on amnesia due to MTLs lesions, in which anterograde amnesia is typically severe. For example, although previous research shows that episodic (autobiographical) memory and EFT are linked, it is not clear to what extent this relates to the fact that episodic memory supplies information retrieved from long-term memory that will be used to construct the novel event, or to the fact that both EFT and episodic memory require associative processes to collate the individual elements of remembered/imagined events. If episodic memories are the building blocks of EFT, then SG should be impaired at imagining personal future events, despite retained anterograde memory abilities, because retrograde amnesia should reduce markedly the number and the variety, of past events from which to draw individual details for event construction. Second, previous research suggests that semantic memory may be sufficient to mediate some forms of event construction. We hypothesize that relatively preserved anterograde memory and semantic knowledge may be sufficient to mediate construction of fictitious experiences with no personal relevance and not located in subjective time.

Finally, we investigated whether impaired EFT in FRA is associated with abnormal attitudes about the future time or steep temporal discounting of future rewards.

Case report

SG is a 49 years old, right-handed man with 10 years of education, who worked as a painter. He was recruited at the Centro studi e ricerche di Neuroscienze Cognitive, Cesena, Italy, in July 2011. In June 2010, at the age of 43, he reported myocardial infarction, followed by cardiac arrest and loss of consciousness. He was still unconscious when admitted at the hospital (Glasgow Coma Scale = 4) and was put in medically induced coma for two days. When drugs were discontinued, he stayed in a state of vigil coma for an additional fifteen days. SG's medical history revealed that he had (untreated) hypertension, and a family history of myocardial infarction. His heart condition and blood pressure are now under control with beta-blockers and aspirin. Brain computed tomography showed a right emicerebellar hypodense area. Structural magnetic resonance imaging (MRI) revealed a perisylvian ventricular expansion, but no signal changes in the brain parenchyma and the structures of the posterior fossa.

The brain insult left SG with a dense retrograde amnesia. He was unable to recall any personal event from his entire life, from childhood to the present days. SG's wife confirmed that he was also unable to recall highly relevant events, such as the birth of their daughters. SG had lost personal semantic information as well. He was unable to report on what his work was, where he lived, what he used to do in his spare time. He could recognize people, as well streets of his hometown, but he did not know why they were familiar, what he had to do with them. He quickly re-learned several aspects of his personal history, and information about his close relatives. It is important to note, however, that re-learning was mainly of facts characterizing relevant lifetime periods (e.g., that he has two daughters, that he is married, that he used to live in another city). SG did not generally re-learn complex, detailed events. Once his wife had recounted to him the details of their first encounter. He could list some of these details to us, but he was clearly not re-

experiencing that event; the story seemed someone else's. SG was quickly able to resume his work as painter: he remembered most of the painting procedures he had practiced for years, and had no problem re-leaning the few he had forgotten. Because of his heart disease, however, SG was forbidden to make excessive physical effort, and therefore his work was (and still is) part-time, and mainly consisting in assisting his colleagues in their activities.

The brain insult made SG a completely different person. According to his wife, SG used to be energetic, lively, at times hyperactive. He wanted to be involved in every family decision and was resolute. He had always faced family problems actively, with a strong sense of responsibility. After the brain insult SG became apathetic, aloof and quiet, with a loss of interest for things he used to enjoy before, such as basketball, his lifelong passion. When questioned about basketball and its rules, indeed, SG showed full knowledge, but no sign of emotion or personal involvement. Apathy is the word that SG's wife uses the most while describing SG: he would spend the whole day watching TV if she did not encourage him to do other activities. He assists his daughters in practical things if he has to, but he does not appear emotionally involved in their lives. He goes to work regularly and actually does work, but he does not seem interested in what he does.

SG is, to some extent, aware of his condition. Soon after the infarction, he would often say that it would have been better for him to die. Shortly after, however, he resigned himself to the situation, treating it simply as a matter of fact. He describes it as "being born again... a new me". At times SG marvels at the extent of his memory loss, but he is unconcerned about his deficit. Occasionally we have seen him irritated by not being able to remember important aspects of his life, but never sorry or regretful.

Given that FRA can be psychogenic in nature, we evaluated circumstances that could have potentially acted as precipitants of amnesia (Ennio De Renzi et al., 1997). An interview with SG's wife revealed that, two years before the infarction, SG's mum had been diagnosed with an aggressive form of cancer, an event that had caused an intense stress to SG. By the time of the infarction, he was still fully involved in assisting her, and often felt overwhelmed by the situation.

This situation caused occasional family conflicts. Besides his mum's illness, SG was generally satisfied with his family and work situation. SG's has no personal history of psychiatric abnormalities, psychopathological traits or alcohol abuse, as confirmed by medical records, and his wife claims he has no family history of psychiatric disease either. After the brain insult, he was seen by a psychiatrist, who noted mild depression and emotional blunting. SG even underwent a few psychotherapy sessions, but these were soon discontinued due to SG's memory problems, which revealed enduring, and impossible to circumvent.

We find it extremely unlikely that SG was feigning amnesia. SG's behavior has always been very consistent. For example, across sessions, he consistently remembers a few episodes from his past, while he consistently fails to access others. When he narrates the events he remembers, he is genuinely proud to be able to share them. SG's wife said she never had the impression that he was pretending to not remember, and that he never "contradicted" himself. On the contrary, at times he would protest vigorously that something he does not remember in fact has not happened, and that she is misremembering things. We do not see evidence for secondary gains from being amnesic in SG. His work activities have been reduced because of his heart problems, but he has always gone to work and has never asked to quit. Also, he does take part in family activities and duties, though with scant personal initiative.

Lesion analysis

We used Voxel Based Morphometry (VBM), a whole brain technique for characterizing regional volume and tissue concentration differences in structural MRI (Ashburner and Friston, 2000, 2001; Good et al., 2001; Mechelli, 2005). SG and fifty healthy control participants (all males; mean age = 40.8 years) underwent the acquisition of high-resolution structural T1-weighted anatomical images with a Philips 3T Intera system (TR = 9.9 ms; TE = 4.6 ms; 170 sagittal slices; voxel size = 1x1x1). Data were analyzed with SPM12 and DARTEL suite (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). The following procedures were applied:

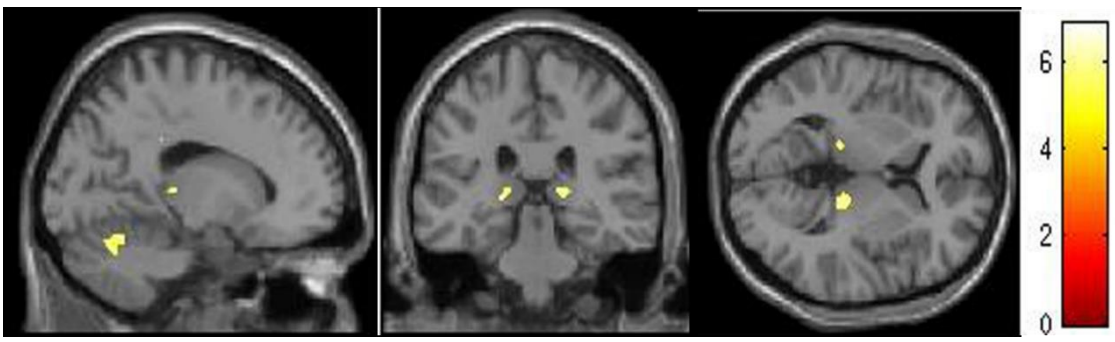
spatial segmentation, template creation, normalization to MNI space and smoothing the resulting modulated GM segments with an isotropic Gaussian kernel of 8x8x8 mm. We accounted for age and global brain volume (total intra-cranial volume) by including these parameters in our 2-sample t test model. At the FWE-corrected threshold of $p < 0.05$, significant areas of reduced grey matter volume were found bilaterally in the fusiform gyrus, thalamus, and cerebellum (see Table 1 and Figure 1). We note, however, that at the threshold of $p < 0.001$, uncorrected, reduced grey matter volume was also detected bilaterally in the hippocampus, the anterior thalamus, and several regions of the autobiographical memory network (Svoboda et al., 2006) (see Supplementary Table and Supplementary Figures). No significant difference was found between patient and controls in white matter volume.

Table 1. Regions of gray matter volume decreased in patient SG ($p < 0.05$ FWE corrected).

	Cluster	Voxel level	MNI coordinates (mm)			Talairach coordinates (mm)		
	k	Z	x	y	z	x	y	Z
L Cerebellum, L Fusiform Gyrus (BA 37, 19)	4917	5.72 5.48	-25 -25	-52 -63	-17 -26	-25 -25	-51 -62	-12 -19
R Cerebellum, R Fusiform Gyrus (BA 19)	1765	5.38 5.3 5.21	26 23 21	-62 -69 -72	-14 -25 -11	26 23 21	-61 -68 -70	-9 -18 -6
R Thalamus (Ventral Posterior Medial Nucleus and Pulvinar)	385	5.06	16	-28	5	16	-27	6
L Thalamus (Ventral Posterior Medial Nucleus and Pulvinar)	89	4.82	-17	-30	4	-17	-39	5

Notes: L = Left; R = Right; BA = Brodmann Area; k = number of voxels.

Figure 1. Regions of decreased gray matter volume in patient SG ($p < 0.05$, FWE-corrected). Clusters are superimposed on the SPM12 template.



Neuropsychological assessment

Tables 2-5 show SG's neuropsychological profile. As is apparent from Table 2, SG showed generally preserved intellectual skills, as revealed by normal performance on the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975), the Wechsler Adult Intelligence Scale (Wechsler, 1981) the Raven Progressive Matrices, and the Verbal Judgment test (for normative data, see (Spinnler and Tognoni, 1987) SG had preserved attentional skills. He attained normal scores on the “Alertness” and the "Divided attention" subtests from the Test battery for Attentional Performance (for normative data, see Zimmermann and Fimm, 2002), and on the Attentional matrices test (Spinnler and Tognoni, 1987). Executive functions were generally preserved, as revealed by the normal scores he obtained in the Stroop test (Spinnler and Tognoni, 1987), the Tower of London test (Culbertson and Zillmer, 2000), verbal fluency measures (Spinnler and Tognoni, 1987), and the Wisconsin Card Sorting Test (WCST, Heaton et al., 2000), though he showed a slightly inflated number of non-perseverative errors. SG also showed a preserved performance in the "Go-NoGo", the "Cognitive flexibility", and the "Spatial incompatibility" subtests of the Test battery for Attentional Performance, which all involve cognitive control and set-shifting abilities (Zimmermann and Fimm, 2002). SG could accurately evoke perceptual details from mental imagery in four out of five tests from Policardi et al. (1996). For example, he could indicate whether animals have a long/short tail, whether letters are mainly made of curved/straight lines, etc., though he was poor at comparing the size of pairs of animals. Short-term memory for both verbal and nonverbal material was within the normal range (Spinnler and Tognoni, 1987), as was working memory, as assessed with the "Working Memory" subtest of Test battery for Attentional Performance (Zimmerman and Fimm, 2002). As for long-term memory, SG had a normal score at the Wechsler Memory Scale (Wechsler, 1988). Spatial long-term memory, as assessed with the Corsi supra-span test and recall of the Rey figure (Spinnler and Tognoni, 1987), was unimpaired. As for verbal long-term memory, SG was unimpaired in prose recall (Spinnler and

Tognoni, 1987), but reported a pathological performance on the Buschke-Fuld Test (Buschke & Fuld, 1974), a standardized selective-reminding list learning task.

Table 2. SG's scores on standardized neuropsychological tests.

	Cut-off	RS	CS	ES
MMSE	24	27	/	N
WAIS-R				
•Verbal	85	64	104	N
•Performance	85	39	91	N
•Total	85	103	98	N
Raven Progressive Matrices	14.75	36	28.50	3
Verbal Judgement test	32	46	42.50	2
Attentional Matrices	30	58	49.25	4
Stroop Test				
• RTs (ms)	27.50	16.50	/	N
• Errors	7.50	0	/	N
Alertness				
RTs (ms)	40	203	60	N
Divided attention				
• RTs (ms)	40	716.50	40	N
• Omissions	40	3	43	N
Go Nogo				
• RTs (ms)	40	575.50	44	N
• False reactions	40	2	43	N
Spatial incompatibility				
• RTs (ms)	40	416.50	53	N
• False reactions	40	4	50	N
Response flexibility				
• RTs (ms)	40	763.50	49	N
• False reactions	40	8	40	N
Working memory				
• RTs (ms)	40	489.50	56	N
• Omissions	40	2	45	N
Verbal Fluency Task				
• Semantic	24	42	44	4
• Phonemic	16	45	46	4
Tower of London				
• Total move score	60	17	112	N
• Rules violation	60	0	104	N
• Execution time	60	104	114	N
WCST				
• Perseverative errors (%)	91	15	100	N
• Non-perseverative err. (%)	91	23	81	B
WMS	85	62.5	106	N
Digit span	3.50	6	5.50	4
Corsi tapping test	3.50	5	5	3
Prose recall	7.50	9.10	8.10	2
Buschke Fuld				
• Consistent Long-Term Retrieval	2	26	-10	0*
• Delayed Retrieval	2	6	4.25	1
Visual Imagery[§]				
• Straight/curved letter task	19.90 (0.32)	20	/	t = 0.30, p = 0.77
• Size comparison of animals' task	29.40 (0.84)	27	/	t = -2.72, p = 0.02*

• Animal tails task	23.60 (1.78)	21	/	t = -1.39, p =0.19
• High/wide object task	28.90 (1.10)	30	/	t = 0.95, p 0.36
• Object color task	27.10 (2.18)	28	/	t = 0.39, p = 0.70

Notes: RS = raw score; CS = corrected score; ES = equivalent score. The ES ranges from 0-4, with 0 = pathological performance, 1 = borderline performance, 2 – 4 = normal performance. N = normal score; P = pathological score; B = borderline score. / = data not available. MMSE = Mini Mental State Examination; WAIS-R = Weschler Adult Intelligence Scale-Revised; WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale. [§]SG's performance at the Visual Imagery Test (Policardi et al., 1996) was compared to that of 10 healthy controls matched in age and education (using Crawford and Garthwaite, 2002). We report healthy controls' means and standard deviations in the table. Impaired performance is highlighted by a (*).

The formal assessment of retrograde memory confirmed an important retrograde amnesia. The Autobiographical Interview was used to probe autobiographical memories established at different times (e.g., Levine et al., 2002; Rosenbaum et al., 2008). The interview requires providing details of a significant one-time episode that was personally experienced at a specific time and place from each of five life periods (childhood, to age 11; adolescence, ages 11–17; early adult life, ages 18–34; middle adult life, ages 35-last year; and the past year). When a specific event was not generated independently, an extensive list of event topics was presented to assist in retrieval. We administered three retrieval conditions: recall, general probe, and specific probe (see Levine et al., 2002). At recall, SG spoke about the event without any interruption from the examiner until he reached a natural ending point. General probes were then used to encourage greater recall of details. At the specific probe phase, a structured interview was administered designed to elicit additional contextual details. SG's reports were recorded, transcribed, and verified by his wife. Author EB, who was blind to the aim of the study, segmented SG's reports into details (unique bits of information), and classified them as internal (episodic) if they related directly to the main event described, were specific to time and place, and conveyed a sense of episodic re-experiencing, or as external (semantic) if they were semantic facts, repetitions, meta-cognitive statements, or unrelated to the main event (Levine et al., 2002). The sum of details in each category was calculated in a cumulative manner for each level of cueing. SG was completely unable to recall any event from the 11-17, 18-34, 35-last year life periods, despite encouraged to use the list of example events (see Table 3). He reported only two salient (negative) past events, one for the childhood decade (when

his brother was born dead) and one for the last year (when he had a car accident). To assess the quality of SG's reports of these events, we compared them to those produced by 10 healthy individuals matched to SG for age and education (all males; mean age = 46.20 years, SD = 6.14, t = 0.12, p = 0.90; mean education = 15.20, SD = 2.49, t = -1.99, p = 0.07), tested in the laboratories of Brian Levine and Shayna Rosenbaum with the same procedure we used. Statistical significance was assessed using individual modified t-tests based on Crawford and Garthwaite's method for comparing single cases with small control samples (Crawford & Garthwaite, 2002). For the childhood event, SG reported fewer internal details than controls, and this difference reached statistical significance at the general (t = -1.91, p = 0.04, one-tailed) and specific probe level (t = -2.01, p = 0.04, one-tailed), though not at free recall (t = -0.97, p = 0.17). The number of external details SG produced was not significantly different from the controls across conditions (p > 0.06 in all cases). The number of internal and external details SG produced for the event from last year was lower than that of the controls, though not significantly so (p > 0.057 in both cases).

Table 3. Number of internal and external details produced at the Autobiographical Interview by SG and controls.

Life epochs	Free recall				General probe				Specific probe			
	Internal details		External details		Internal details		External details		Internal details		External details	
	SG	HC	SG	HC	SG	HC	SG	HC	SG	HC	SG	HC
0-11 years	3	11.9 (2.75)	1	6.2 (0.96)	3*	22.3 (3.03)	1	14.8 (3.84)	22*	59 (5.56)	16	30.5 (5.57)
Last year	11	21.6 (7.58)	8	13 (4.63)	11	34.4 (6.82)	13	16.6 (4.62)	19	74.9 (9.64)	17	30.1 (4.93)

Notes: HC = healthy controls. The values in parentheses are standard errors of the mean. Asterisks highlight statistically significant differences between GS and controls. Note that SG was unable to produce any event for the 11-17 years, 18-34 years, and 35-second to last year time periods.

Several tests were used to assess memory for famous remote events and people. The Italian Questionnaire for Remote Events (Budriesi et al., 2002) probes knowledge for events extensively covered by the media in each of four 4-year periods: from 1994-1997 (Q1, the most recent 4-year period) to 1966-1969 (Q8, the most remote 4-year period), for a total of 64 items. In each item, the

patient is required to indicate the correct response among four alternatives (e.g. “Where did the 1996 Olympic games take place: Atlanta, Minneapolis, Los Angeles, or San Francisco?”). The test demands participants to be at least 16 years old at the time events occurred, and therefore SG was administered periods Q1 to Q3. SG reported a pathological overall score (see Table 4), with a significantly impaired performance on facts from 1990 to 1993. The Media Mediated Memory Test (Bizzozero, Lucchelli, Prigione, Saetti, & Spinnler, 2004) consists of 65 items concerning famous public events occurred from 1976 to 2000. The test is first administered following a free recall procedure ("What happened to John Lennon?"). If the participant fails to recall any information about a famous event spontaneously, one or two cues relating to some key aspects of the to-be-recalled event are provided (e.g. “He was a member of a famous pop band”, “He was killed in New York”). SG's score was below the normal range (see Table 4). The Famous Face and Name Test (Rizzo, Venneri, & Papagno, 2002) requires recognizing famous people from their face or name. In each of 100 (50 famous, 50 non-famous) face and 100 (50 famous, 50 non-famous) name trials, the patient has to provide a fame judgment and semantic information about famous people. SG could normally recognize famous faces and names (see Table 4). The General Knowledge of the World Test (Mariani, Sacco, Spinnler, & Venneri, 2002) assesses two domains of semantic memory: incidental knowledge, comprising 8 domains (e.g., famous past events, famous people, structural and functional knowledge about natural and artificial elements, crafts, popular culture, e.g., “What does a farmer do?”), and encyclopedic knowledge, including 6 domains (history, geography, science, politics, arts, mathematics, e.g., “What do you know about Dante Alighieri?”). There were 12 items for each domain, for a total of 168 items. SG's encyclopedic knowledge was impaired, but incidental knowledge was normal (see Table 4). We found no evidence of malingering at the Digit Memory Test (Barletta-Rodolfi, Ghidoni., & Gasparini, 2011, see Table 4).

Table 4. SG's scores on retrograde memory tests.

	Cut-off	RS	CS	ES
MEF				
1994-1997	3.57	4	3.99	N
1990-1993	3.99	2	1.90	P*
1986-1989	3.53	6	5.90	N
QM	-1.74	/	-2.17	P*
MMMT				
Total score	66.80	60	44.77	0*
FFT				
Face recognition				
• Denomination	14.50	19	21.75	2
• Semantic	22.17	29.25	31	2
Name recognition				
• Semantic	20.68	42.25	40.75	4
GKW				
• *Incidental Knowledge*	646.30	858	655	N
	403.50	471	218.75	P*
• *Encyclopedic Knowledge*				
DMT	36	71	/	N

Notes: RS = raw score; CS = corrected score; ES = equivalent score. The ES ranges from 0-4, with 0 = pathological performance, 1 = borderline performance, 2 – 4 = normal performance. N = normal score; P = pathological score; B = borderline score. / = data not available. MEF = Italian Questionnaire for Remote Events; MMMT = Media Mediated Memory Test; FFT = Famous Face Test; GKW = General Knowledge of the World Test; DMT = Digit Memory Test for malingering. Impaired performance is highlighted by a (*).

We also assessed SG's mood and affective state (see Table 5). SG showed borderline levels of depression at the Beck Depression Inventory (BDI-II; Beck et al., 1996), but absence of depression in two additional scales: the Hamilton rating scale for Depression (HAM-D; Hamilton, 1960), and the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983). Both state and trait anxiety were normal at the State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983). SG also showed normal levels of positive and negative emotions in the Positive and Negative Affect Schedule (PANAS; Zevon and Tellegen, 1982; Watson et al., 1988), a measure of general affective states comprising a list of 20 emotions, and requiring to rate the extent to which each of the emotions was experienced over the past week on a 5-point Likert Scale.

Table 5. Assessment of SG's mood and affective responses.

	Cut-off	RS	CS	ES
BDI-II	5	5	/	B
HAM-D	20	3	/	N
HADS				
• Anxiety	8	1	/	N
• Depression	8	4	/	N
STAI				
• State	61.44	25	/	N
• Trait	61.04	38	/	N
PANAS				
• Positive affect	29.10	31	/	N
• Negative affect	16.30	10	/	N

Notes: RS = raw score; CS = corrected score; ES = equivalent score. The ES ranges from 0-4, with 0 = pathological performance, 1 = borderline performance, 2 – 4 = normal performance. N = normal score; P = pathological score; B = borderline score. / = data not available. BDI-II = Beck Depression Inventory; HAM-D = Hamilton rating scale for Depression; HADS = Hospital Anxiety and Depression Scale; STAI = State Trait Anxiety Inventory; PANAS = Positive and Negative Affective Scale. Impaired performance is highlighted by a (*).

Experimental investigation

SG was administered a series of tasks/questionnaires aimed at probing different aspects of future thinking, attitudes about the future, and future-based decision-making. Note that participants in the control sample were not completely overlapping across tasks, and therefore will be described for each task separately. Participants gave informed consent, according to the Declaration of Helsinki (International Committee of Medical Journal Editors, 1991) and the Ethical Committee of the Department of Psychology, University of Bologna. To compare SG's performance to that of healthy controls, we used individual modified t-tests based on Crawford and Garthwaite's (Crawford & Garthwaite, 2002) method for comparing single cases with small control samples. Statistical significance was set at $p < 0.05$, two-tailed.

Construction of future and fictitious experiences

Participants. SG and 10 healthy individuals (all males) matched for age and education (mean age = 46.00 years, SD = 3.83; mean education = 12.00 years, SD = 1.76) underwent a scene construction task modified from Hassabis et al. (2007b) (see also Bertossi et al., 2016a).

Task. Participants constructed novel experiences in as much detail as possible in response to short cue descriptions (read by the experimenter), referring to eight scenarios. Five scenarios

require constructing fictitious experiences, with no requirement for mental time travel and not explicitly self-relevant ("fictitious scenarios", e.g., "Imagine you're standing in the middle of a bustling street market. I want you to describe the experience and the surroundings in as much detail as possible using all your senses including what you can see, hear and feel"). Fictitious scenarios were the 'market', 'port', 'museum', 'pub' and 'forest' scenarios used in Hassabis et al. (2007b). Differently, three scenarios required constructing plausible personal future experiences (future scenarios; e.g., "Imagine the next time you'll meet a friend. I want you to describe the experience and the surroundings in as much detail as possible using all your senses including what you can see, hear and feel"). These corresponded to the 'next meeting with a friend', 'next weekend' and 'next Christmas' scenarios from Hassabis et al. (2007b; see also Bertossi et al., 2016a). Participants described the imagined experiences until they came to a natural end. The examiner was allowed to use general probes aimed at encouraging further description and make sure participants felt like anything else could be added (e.g., "can you see anything else in the scene?"), but could not introduce any concept not mentioned by the subject. For all scenarios, participants were explicitly told not to recount a memory but to create something new. After each scenario, participants rated the constructed experiences across a number of different categories, including sense of presence (from 1 = 'I did not feel like I was there at all' to 5 = 'I felt strongly like I was really there'), perceived salience (from 1 = 'I couldn't really see anything' to 5 = 'extremely salient'), perceived detailedness (from 1 = 'not detailed at all' to 5 = 'very detailed'), task difficulty (from 1 = 'very easy' to 5 = 'very difficult'), and similarity to a memory (from to 1 = 'exactly like a memory' to 5 = 'not at all like a memory'). Finally, participants were presented with a list of twelve sentences and had to state whether each sentence described or not their image of the scenario (e.g., I could see it as one whole scene in my mind's eye). These probe questions were designed to estimate the spatial integrity of the scene. Testing sessions were digitally recorded to enable transcription and later scoring of participants' reports.

Scoring. Participants' records were scored as in Hassabis et al. (2007b). For each trial, we calculated an 'experiential index' (EI) indicating the overall richness of the constructed experience. The EI ranges between 0 and 60, as it is calculated as the sum of four subcomponents: content (score ranges between 0 and 28), participant ratings (sum score from two scales, perceived salience and sense of presence, ranges between 0 and 8), spatial coherence index (score ranges between 0 and 6) and quality judgment (score ranges between 0 and 18). For the content score, each scenario description was segmented into a set of statements. Every statement was classified as belonging to one of four categories: entities present (EP, objects, people, animals present in the scenarios), sensory descriptions (SD, statements describing the properties of an entity, e.g., 'the chair is made of wood'), spatial references (SPA, statements regarding the relative position of entities within the environment, directions or explicit measurements, e.g., 'behind the bar', 'to my left') and thoughts/emotions/actions (TEA, e.g., 'I left', 'I was lonely'). For each subcategory, details were summed and the score was capped at a maximum of 7 (as in Hassabis et al., 2007b) (but we obtain similar results if we use the uncapped data). Therefore, the total possible content score for each experience was 28. The 'spatial coherence index', a measure of the spatial integrity of the imagined scene, was derived from the responses to 12 questions requiring participants to describe the "spatial quality" of the experiences they had constructed: 8 statements indicated that aspects of the scene were integrated (e.g. 'I could see it as one whole scene in my mind's eye'), and 4 statements indicated that aspects of the scene were fragmented (e.g. 'It was not so much a scene as a collection of separate images'). One point was assigned for each integrated statement selected and one point was subtracted for each fragmented statement selected. These values were summed but rescaled (normalized around zero) to range between -6 (spatially fragmented) to 6 (spatially coherent). Only positive values, however, were included in the EI so as not to over penalize fragmented descriptions (as in Hassabis et al., 2007b). Participants' ratings of sense of presence and perceived salience, each originally ranging from 1 to 5, were rescaled to range from 0 to 4 before being included in the EI. The quality judgment is the scorer's assessment of the overall quality of the constructed experience.

The scorer was requested to rate how well she felt the description induced a detailed “picture” of the scenario in her own mind's eye. Originally ranging from 0 (no picture at all) to 10 (extremely rich picture) to avoid a complicated rating, the quality judgment was rescaled between 0 and 18 to be included in the EI. We calculated the EI separately for fictitious and future scenarios. Author EB, who was blind to the aim of the study and to participants' identity (SG vs. controls), scored all the scenarios.

Results. Figure 2 shows the EI by type of scenario in SG and the controls, and Table 6 details the scores attained in the subcomponents of the EI (see Supplementary Materials for examples of constructed future and fictitious experiences in SG and a healthy control subject). As is apparent from Figure 2, SG reported a significantly lower EI than healthy controls for future scenarios ($t = -2.62$, $p = 0.03$), but not for fictitious scenarios ($t = -0.20$, $p = 0.85$). To investigate the origin of SG's scene construction deficit and of the apparent discrepancy in his performance with future vs. fictitious scenarios, we analyzed all the subcomponents of the EI separately (see Table 4). As for the content score, SG reported significantly fewer thought/emotion/action details (TEA) than controls for future ($t = -2.59$, $p = 0.03$), but not for fictitious scenarios ($t = -0.93$, $p = 0.38$). In contrast, the number of sensory details (SD), entities present (EP) and spatial references (SPA) was comparable between SG and the controls, for both future ($p > 0.07$ in both cases) and fictitious scenarios ($p > 0.8$ in both cases). As for subjective ratings, SG reported a lower perceived salience than controls for future ($t = -4.46$, $p = 0.002$), but not for fictitious scenarios ($t = 1.31$, $p = 0.22$). In contrast, SG's sense of presence was lower than controls for both future ($t = -5.57$, $p < 0.001$) and fictitious scenarios ($t = -4.99$, $p = 0.001$). The spatial coherence index ($p > 0.08$ in both cases) and the quality judgment ($p > 0.38$ in both cases) were not significantly different between SG and the controls, for both future and fictitious scenarios. We also looked at task measures not involved in the EI. SG found future ($t = 2.50$, $p = 0.03$) but not fictitious ($t = 0.34$, $p = 0.74$) scenarios more difficult than did controls, and rated future ($t = -3.91$, $p = 0.004$) but not fictitious ($t = -0.61$, $p = 0.56$) scenarios to be less detailed than those of the controls. Self-ratings of similarity to

memory for future (p = 0.06) and fictitious scenarios (p = 0.77) were not significantly different between SG and the controls. To compare directly the differences in imagining fictitious and future experiences across participants, we calculated Δ scores for the EI and all its subcomponents as the difference in performance for fictitious vs. future scenarios. The Δ_{EI} was significantly higher in SG than in controls (16.39 vs. 4.51, t = 2.51, p = 0.03), as were the Δ scores for the spatial coherence index (2.07 vs. -0.07, t = 3.46, p = 0.007), and for perceived salience (2.53 vs. -0.19, t = 5.89, p < 0.001). Differences between SG and controls in Δ scores for the other subcomponents of the experiential index, or variables not included in the EI, did not reach statistical significance (p > 0.054 in all cases).

Future vs. fictitious cues. Although future and fictitious cues were generally matched in difficulty (t = 0.79, p = 0.45), we note that some of the fictitious cues contained information that may have been useful to prime associations in SG (e.g., a *bustling* market) (see also Bertossi et al., 2016a). Indeed, in general, healthy controls produced more details (i.e., total content score) for fictitious compared to future scenarios (t = 2.64, p = 0.03). We therefore focused on a subset of future (N = 2) and fictitious scenarios (N = 3) for which controls produced a similar number of details (t = 0.28, p = 0.79), and had a similar EI (t = 0.50, p = 0.63). Even when we restricted our analyses to these scenarios, we confirmed that SG, compared to controls, had a reduced EI for future (t = -2.40, p = 0.04) but not fictitious scenarios (t = - 0.48, p = 0.64), and a higher Δ_{EI} (t = 4.55, p = 0.001). This finding suggests that SG's worse performance with future vs. fictitious scenarios was not driven by differences in the quality of the cues.

Figure 2. Experiential index for future and fictitious experiences in SG and healthy controls. * = $p < 0.05$.

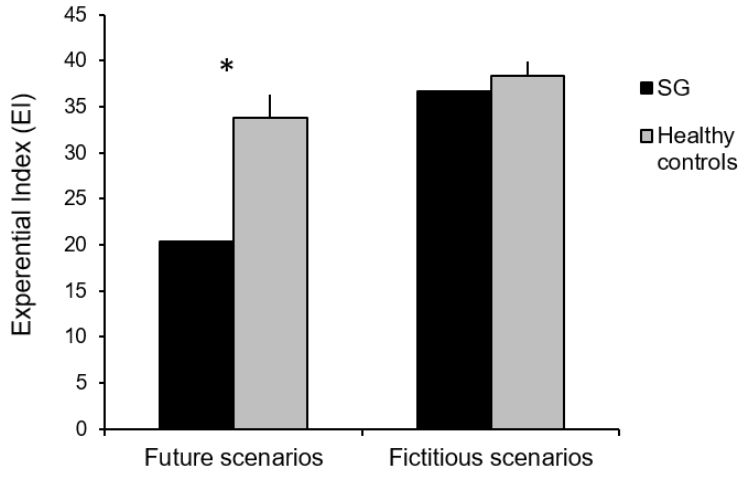


Table 6. SG's constructed experience performance.

	Future scenarios		Fictitious scenarios	
	SG	HC	SG	HC
Experiential Index	20.33*	33.82 (1.55)	36.72	38.33 (2.44)
Contents:				
Entities Present (EP)	1.67	3.47 (0.41)	5.00	5.22 (0.34)
Spatial References (SPA)	3.33	2.97 (0.33)	2.80	2.78 (0.55)
Thoughts/Emotions/Actions (TEA)	6.00*	6.87 (0.10)	5.40	6.24 (0.27)
Sensory Descriptions (SD)	1.33*	3.97 (0.40)	5.80	5.52 (0.36)
Ratings:				
Sense of presence	1.00*	2.87 (0.10)	0.60*	2.64 (0.12)
Perceived salience	0.67*	2.73 (0.14)	3.20	2.54 (0.15)
Spatial Coherence Index	0.33	2.73 (0.41)	2.40	2.66 (0.46)
Quality Judgment	6.00	8.22 (0.72)	11.52	10.73 (0.75)
Ratings not involved in the EI:				
Detailedness	1.00*	2.27 (0.10)	1.80	2.24 (0.22)
Difficulty	3.33*	1.60 (0.21)	2.00	1.76 (0.21)
Similarity to a memory	3.67*	1.77 (0.27)	2.80	2.64 (0.16)

Notes. HC = healthy controls. The values in parentheses are standard errors of the mean. Significant differences between SG and the controls are highlighted by a (*).

Attitudes about future time

Participants. SG and 10 healthy individuals (all males) matched to SG in age and education (mean age = 49.40 years, SD = 6.26; mean education = 11.60 years, SD = 3.20) underwent the Consideration of Future Consequences scale (Strathman, Gleicher, Boninger, & Edwards, 1994) and the Future Time Perspective scale (Carstensen and Lang, 1996).

Task. The Consideration of Future Consequences scale is a measure of the extent to which individuals consider (and are influenced by) the distant outcomes of current behavior. Individuals high in consideration of future consequences focus more on the future implications of their behavior and use these to inform choices (e.g., 'I am willing to sacrifice my immediate happiness in order to achieve future outcomes'), whereas individuals low in consideration of future consequences focus more on immediate needs and concerns (e.g., 'I only act to satisfy immediate concerns, figuring that I will take care of future problems that may occur at a later date'). The Consideration of Future Consequences scale consists of 12 items measured on a Likert scale ranging from 1 (extremely uncharacteristic of me) to 5 (extremely characteristic of me), to range from 12 to 60. High scores indicate high consideration of future consequences. The Future Time Perspective scale measures the tendency to think in terms of the future. Individuals high in future time perspective focus on future opportunities and perceive a distant end (e.g., 'I expect that I will set many new goals in the future'), whereas individuals low in future time perspective focus on future limitations and perceive a near end (e.g., 'I have the sense time is running out') (Cate & John, 2007). The Future Time Perspective scale includes 10 items measured on a Likert-type scale ranging from 1 (extremely uncharacteristic of me) to 7 (extremely characteristic of me), to range from 10 to 70. High scores indicate an extended future time perspective.

Results. Table 7 shows the scores attained at the Consideration of Future Consequences scale ($t = -1.06$, $p = 0.31$) and the Future Time Perspective scale ($t = 0.80$, $p = 0.44$) by SG and the controls, which were not significantly different.

Delay discounting

Participants. SG and 12 healthy individuals (all males) matched to SG for age and education (mean age = 44.25 years, SD = 4.20; mean education = 11.50 years, SD = 2.02) were administered a computerized delay discounting task.

Task. The delay discounting task required participants to choose between an amount of (hypothetical) money that could be received immediately and an amount of money that could be

received after some specified delay (Myerson et al., 2001; Sellitto et al., 2010). Participants made five choices at each of six delays: 2 days, 2 weeks, 1 month, 3 months, 6 months, 1 year. The order of blocks of choices pertaining to different delays was randomly determined across participants. Within each block of five choices, the first choice was between a delayed amount of 40 units and an immediate amount of 20 units. The delayed amount was always 40 euros, whereas the amount of the immediate reward was adjusted based on the participant's choices, using a staircase procedure that converged on the amount of the immediate reward that was equal, in subjective value, to the delayed reward. To estimate the rate at which the subjective value of a reward decays with time, we calculated two indices: the delay discounting parameter *k* and the area under the empirical discounting curve (AUC) (Myerson et al., 2001). To estimate *k*, the hyperbolic function $SV = 1/(1+kD)$, where SV = subjective value (expressed as a fraction of the delayed amount), and D = delay (in days), was fit to the data to determine the *k* constant of the best fitting delay discounting function, using a nonlinear least-squares algorithm. The larger the value of *k*, the steeper delay discounting, the more participants were inclined to choose small-immediate rewards over larger-delayed rewards. To calculate AUC, delays were expressed as a proportion of the maximum delay (360 days), and subjective values were expressed as a proportion of the delayed amount (40 euros). Delays and subjective values were then plotted as x and y coordinates, respectively, to construct a discounting curve. Vertical lines were drawn from each x value to the curve, subdividing the area under the curve into a series of trapezoids. The area of each trapezoid was calculated as $(x_2-x_1)(y_1+y_2)/2$, where x_1 and x_2 are successive delays, and y_1 and y_2 are the subjective values associated with these delays. The AUC is the sum of the areas of all the trapezoids and varies between 0 and 1. The smaller the AUC, the steeper delay discounting.

Results. The hyperbolic model described the discounting behavior of SG and the controls equally well, as revealed by comparable R^2 scores (0.71 vs 0.55, t = 0.38, p = 0.71). There was no difference in delay discounting rates between SG and the controls, either in (log-transformed) *k* values (t = 0.20, p = 0.84) or the AUC (t = -0.33, p = 0.75) (see Table 7). These results held, for

both *k* (t = 0.44, p = 0.67) and AUC (t = -0.31, p = 0.76), even when we removed a significant outlier from the controls sample, who showed extremely steep delay discounting.

Table 7. Attitudes about future time and future based decision-making.

	CFC Scale	FTP Scale	k (log)	AUC
Patient SG	35	50	-1.48	0.37
HC	42.00 (1.98)	42.10 (3.01)	-1.80 (0.44)	0.48 (0.09)

Notes: HC = healthy controls, CFC = Consideration of future consequences scale, FTP = Future time perspective scale. AUC = Area under the discounting curve. The values in parentheses are standard errors of the mean.

Discussion

This study investigated episodic future thinking (EFT) and future-based cognition and decision-making in a patient, SG, who developed FRA following hypoxia due to a cardiac arrest. SG became unable to recall personal experiences from his entire lifetime, with virtually no evidence of a temporal gradient. At the Autobiographical Interview, SG could only think of two extremely salient negative events (one from childhood and one from the last year) and recalled them with few details. SG had a mixed semantic memory profile, with impaired personal semantic knowledge (that he could, however, re-acquire), preserved memory for famous people but not famous events, and a generally spared semantic knowledge base, except for some instances of encyclopedic knowledge (e.g., history, mathematics). A severe loss of pre-traumatic episodic recollection, combined with a "patchy" profile of reduced and preserved ability to semantically know about events, people, and facts from the pre-traumatic past is one of the most frequent presentations of FRA (Wheeler and McMillan, 2001). Here we show that, in addition to the inability to recollect pre-traumatic events, SG was unable to imagine personal future events. SG, however, did not have a pervasive inability to imagine experiences, as he could imagine fictitious events not located in subjective time and not self-relevant. Moreover, SG's impaired EFT did not translate into an overall inability to conceive the future time: SG showed normal time perspective, consideration of future options, and delay discounting rates for future rewards.

One first issue to discuss is the origin of SG's FRA. Voxel-based morphometry revealed multifocal reductions of gray matter volume, most pronounced in the fusiform gyrus, the cerebellum, and the posterior thalamus bilaterally, suggesting an organically based amnesia. This is, however, not a typical location of neuropathology for FRA. Most cases of FRA with more severe episodic than semantic deficits, as is SG, have damage to the anterior temporal and frontal cortices (Kapur et al., 1992; Markowitsch et al., 1993; Calabrese et al., 1996; Kroll et al., 1997; Levine et al., 1998), and, less often, the MTLs (Kapur et al., 1996; Fujii et al., 1999; Tanaka et al., 1999; Grilli et al., 2017). FRA has been occasionally observed following posterior lesions confined to the temporo-occipital, occipital, and parietal cortex (O'Connor et al., 1992; Ogden, 1993; Schnider et al., 1994; Hunkin et al., 1995), often in association with visual imagery deficits. The fusiform gyrus, reduced in volume in SG, connects the striate cortex to the inferior temporal cortex, which has been considered a possible long-term store site for visual information (Mishkin, 1982). It has been suggested that autobiographical memory primarily requires retrieval of detailed visual features of the event, which would then in turn reactivate also non-visual details, conceptual knowledge, and emotions related to the event (Rubin and Greenberg, 1998). One possibility, then, is that the reduction of fusiform gyrus volume hindered the reinstatement or re-visualization, of old memories. The fusiform gyrus, indeed, is activated during autobiographical memory retrieval (Gilboa et al., 2004; Svoboda et al., 2006) and patients with (psychogenic) FRA may show temporo-occipital hypometabolism (Thomas-Antérion et al., 2010, 2014; Hennig-Fast et al., 2008). The evidence that SG performs well on most tests of visual imagery, and that he can imagine complex fictitious experiences, however, makes it unlikely that his FRA was fully explained by the lesion in the fusiform gyrus. Moreover, SG has also lost knowledge about public past events, which depends less on visualization than autobiographical memory, while he has preserved famous face recognition, and the fusiform gyrus is deemed critical for face processing (Kanwisher et al., 1997).

The cerebellum, another region reduced in volume in SG, is considered a component of the autobiographical memory network (Maguire, 2001; Svoboda et al., 2006), possibly due to its

connections to the dorsolateral prefrontal cortex via the cerebello-thalamocortical pathway (Middleton and Strick, 1994). The cerebellum is also activated during EFT (Addis, Wong, & Schacter, 2007; Szpunar, Watson, & McDermott, 2007). The most common neuropsychological deficits following cerebellar lesions, however, include impairments of attention, executive functions, and working memory (see Schmahmann and Sherman, 1998; Vokaer et al., 2002; Ravizza et al., 2006; Chiricozzi et al., 2008), which SG does not show. Moreover, although anterograde memory deficits are a common consequence of cerebellar damage (Nakamoto et al., 2014), we are not aware of cases of retrograde amnesia. We suspect, therefore, that although the reduction in volume of the cerebellum may have contributed to SG's mild anterograde amnesia, it is not responsible for his important retrograde amnesia, especially in the context of preserved executive functions. Damage to the thalamus has also been associated with amnesia (Gentilini et al.,1987; Stuss et al., 1988). The (anterior) thalamus, indeed, receives both direct (via the fornix) and indirect (via the mammillary bodies and mamillo-thalamic tract) projections from the hippocampus (Aggleton & Brown, 1999). Unlike SG, however, most patients with thalamic amnesia have a prevalent deficit of anterograde memory (see Carlesimo et al., 2011, for a review), although cases of retrograde autobiographical amnesia have been described (e.g., Goldenberg et al., 1983; Stuss et al., 1988; Hodges and McCarthy, 1993; Markowitsch et al., 1993). Moreover, thalamic amnesia is strongly predicted by the involvement of the anterior and the medio-dorsal nuclei (Carlesimo et al., 2011), while SG has reduced volume in the posterior nucleus. Thus, although the volumetric reduction of the fusiform gyrus, cerebellum, and thalamus may explain some aspects of SG's mnemonic profile, it is unlikely that it fully explains his FRA. We note that (at a lower threshold) SG has additional volume reductions in several regions of the autobiographical memory network, including the hippocampus and the posterior cingulate and temporal cortex. These regions have been consistently associated with autobiographical memory (Svoboda et al., 2006; Philippi et al., 2015), and their damage with FRA (Wheeler and McMillan, 2001; Fast and Fujiwara, 2001). This extended neuropathology likely underlies SG's FRA.

Considering some circumstances of SG's clinical history, and the fact that SG's brain abnormalities are not typically associated with retrograde amnesia, we considered the possibility that his FRA was psychogenic in nature. SG's mother illness was an emotionally loaded event that SG was barely able to bear, and could have acted as a precipitating event, though psychogenic amnesia is most typically triggered by adverse life conditions of recurrent nature, with onset in childhood/early adulthood, and a stronger impact on identity (Reinhold and Markowitsch, 2009; Staniloiu and Markowitsch, 2012). Personality changes as those observed in SG are also very frequently associated with psychogenic amnesia, as are the relative lack of concern for one's deficits and the loss of interest for premorbid activities (Staniloiu and Markowitsch, 2012). The diagnosis of psychogenic amnesia, however, additionally requires the presence of a past history of psychiatric disorders, or at least a hint that the patient had a tendency to escape life difficulties by refuging into psychosomatic complaints (De Renzi et al., 1997; Kopelman et al., 1994; Kihlstrom and Schacter, 2000). SG had no psychiatric history and used to be a very responsible and stable man. His apathy and lack of initiative may derive from amnesia itself: from not remembering what he used to do and is supposed to initiate, from not being able to conceive his future. Most probably, SG's clinical presentation is the result of an organic factor (an important brain insult, with protracted loss of consciousness) superimposed on a background of already increased stress responses, magnifying the behavioral consequences (see also Staniloiu and Markowitsch, 2012).

An interesting finding of the present study is the intricate pattern of SG's preserved and impaired imaginative and prospection abilities. First of all, SG's loss of autobiographical memory came along with an impairment in imagining personal future experiences, consistent with the hypothesis that (fragments of) episodic memories serve as the building blocks of EFT (Buckner and Carroll, 2007; Schacter et al., 2008; Schacter et al., 2012). We found, indeed, that SG's constructed experience contained few actions, emotions, and thoughts compared to the controls. SG himself found EFT difficult and rated his constructed future experience as poor in salience and detailedness. In general, individuals tend to rely on past experiences as source of detail during EFT, especially

when they find EFT effortful. Having lost most of his autobiographical memories, SG now relies on a heavily reduced source of details to construct EFT. An important question is how SG managed to construct complex fictitious experiences, a task that amnesic patients cannot do (Hassabis et al., 2007). We suggest that relatively preserved semantic memory and anterograde memory may be critical in SG's execution of this form of event construction. SG may use his preserved semantic and world knowledge to conceive how events may logically unfold in commonplace scenarios (e.g., a market, a port), without the need to resort to autobiographical memory. Note that SG's anterograde memory, though weak, was sufficient for him to re-learn several aspects of his past and therefore clearly functional. This warranted the successful assembly of details (retrieved primarily from semantic memory) into the novel fictitious experiences (Mullally et al., 2014). At odds with amnesic patients, indeed, SG has a normal spatial coherent index, which suggests he may succeed at creating an initial, sketchy scene, as expected considering that his hippocampus is not damaged, but only slightly reduced in volume (i.e., at a lower threshold). He is then able to fill that initial scene with (mostly semantic) information to construct fictitious scenarios, but falls short of details while constructing EFT, which is more dependent on access to autobiographical memory than is construction of fictitious events. Vivid and plausible personal future events, indeed, are frequently set in familiar places (Arnold et al., 2011; de Vito et al., 2012; Robin and Moscovitch, 2014; Robin et al., 2015) and informed by knowledge about oneself and close others (D'Argembeau and Mathy, 2011). SG's comments during scene construction were telling with respect to the (semantic) strategy he used to construct fictitious experiences, and its insufficiency for EFT. While constructing a fictitious experience he said: “We are in a forest, beside a river, so there must be a lot of green around”. While trying to imagine his next Christmas day, however, he said, literally: “Sure, there must be relatives, gifts ... but I cannot visualize it, because I do not know how to remember it”. That he resorted to a semantic strategy while constructing experiences is also consistent with the fact that he self-reported a low sense of presence not only for future but also for fictitious experience, as if he could not actually project himself even into experiences he could conceive.

SG shares a number of similarities with amnesic patient P01 from Hassabis et al. (2007), but he is also different from P01. Both suffer from a profound impairment of episodic memory with relatively spared semantic memory, and both can count on some residual anterograde memory abilities. Despite both patients can construct fictitious experiences, they differ in their ability to construct future experiences, which is normal in P01, and impaired in SG. This difference may relate to the fact that P01 had intact personal semantics, whereas SG had initially lost personal semantic information as well, though he could re-learn several aspects of it. We have never had the impression that, even after such massive re-learning, SG actually rescued his personal history. He recites it much like a student does with the biography of a famous person. Personal knowledge is crucial to drive autobiographical remembering and EFT (D'Argembeau & Mathy, 2011), and may be not sufficiently functional in SG.

Interestingly, SG's FRA and impaired EFT did not make him stuck in the present time. Similarly to amnesic patients with MTLs damage (Kwan et al., 2012, 2013; Craver et al., 2014), he proved able to think in terms of the future, and consider the distant outcomes of his behavior. Moreover, SG showed normal delay discounting rates during intertemporal choice, indicating he was not abnormally biased toward smaller-immediate over larger-delayed rewards. This finding is additional evidence that, although decision-making often involves EFT (Suddendorf & Corballis, 2007), and EFT can reduce delay discounting (Peters and Büchel, 2010; Benoit et al., 2011), EFT is just one of several mechanisms to conceive the future. As such, EFT is not necessary to achieve future-oriented decision-making, which can be based on alternative, semantically-based, mechanisms to orient in time.

To conclude, the study of case SG confirms the close relation between autobiographical memory and EFT, while revealing that some forms of event construction and some forms of prospection can withstand severely impaired retrograde memory abilities. Together, these findings enrich our understanding of the component processes of mental time travel and of the fractionation of human temporal consciousness.

Chapter 2.

Episodic future thinking following vmPFC damage.

In this chapter, I begin to explore the neural basis of the mental construction of future events. As neuroimaging studies have extensively demonstrated that the ventromedial prefrontal cortex (vmPFC) is part of a network of regions involved in episodic memory and episodic future thinking (EFT), here I will investigate whether vmPFC is necessary for EFT, by comparing EFT in vmPFC patients and healthy controls. To begin to clarify the role of vmPFC in EFT, I will explore whether nonepisodic mechanisms, namely, narrative and working memory abilities, have an impact on vmPFC patients' event construction deficits.

Study 2. Episodic future thinking following vmPFC damage: impaired event construction, maintenance, or narration?

Co-authored with Elena Bertossi, Vanessa Candela, and Elisa Ciaramelli.

(Bertossi E, Candela V, De Luca F, Ciaramelli E. 2017. 31(3):337-348. *Neuropsychology*)

Introduction

Humans have the ability to conceive events that differ from those unfolding in the present, and a particular propensity to imagine events that may happen to them in the future (D'Argembeau, Renaud, & Van der Linden, 2011). Functional MRI (fMRI) studies have shown that EFT engages a "core network" of brain regions that are also activated by episodic memory, including the ventromedial prefrontal cortex (vmPFC), posterior cingulate cortex (PPC), angular gyrus and medial temporal lobes (MTLs; Okuda et al., 2003; Addis, Wong, & Schacter, 2007; Szpunar, Watson, & McDermott, 2007). Coherently, patients with lesions in key nodes of this network, such as the MTLs (Race, Keane, & Verfaellie, 2011; Romero & Moscovitch, 2012; Rosenbaum, Gilboa, Levine, Winocur, & Moscovitch, 2009), vmPFC (Bertossi, Aleo, et al., 2016; Bertossi, Tesini, et al., 2016; but see Kurczek et al., 2015), and parietal cortex (Berryhill et al., 2007; Berryhill et al.,

2010), may show a deficit in EFT that parallels that shown in episodic remembering. The overlap in the neural bases of EFT and episodic remembering may relate to the common component processes of the two activities, which both require constructive processes needed to recover and integrate the individual elements composing the remembered/imagined event (i.e., episodic simulation; Schacter and Addis, 2007) or to generate, maintain and visualize its spatial context (i.e., scene construction; Hassabis & Maguire, 2007). Differences in brain activity between remembering and imagining have also emerged, which contribute to reveal additional component processes of EFT. For example, the frontopolar, dorsolateral, and lateral temporal cortices are more active during construction of future compared with past events (Addis et al., 2007; Okuda et al., 2003). EFT requires recombining flexibly details from multiple episodes as well as semantic memory into an event not experienced before (Schacter et al., 2012). These operations likely depend on executive functions, in line with the engagement of the dorsolateral prefrontal cortex (Addis et al., 2007). Studies involving patients with brain damage affecting either the integrity or the function of the prefrontal cortex provide support to this hypothesis. Patients with Parkinson's disease, for example, show preserved episodic remembering but impaired future thinking, and the degree of impairment correlated with executive functioning (de Vito et al., 2012). EFT is related to executive functioning also in healthy individuals (D'Argembeau, Ortoleva, Jumentier, & Van der Linden, 2010). The frontopolar cortex, has long been implicated in forming and maintaining intentions (Burgess, Quayle, & Frith, 2001), and its activity correlated with the number of references to intentions (Okuda et al., 2003). Moreover, this region processes information about personal goals (D'Argembeau et al., 2010), and therefore may be crucial to drive construction of one's personal future (D'Argembeau & Mathy, 2011). Interestingly, although frontotemporal dementia causes a similar impairment in episodic remembering and future thinking, patients' EFT deficits are mainly associated with atrophy in the frontopolar cortex, whereas retrieval deficits correlated with atrophy in medial prefrontal regions (Irish, Hodges, & Piguet, 2013). EFT is also more heavily reliant on semantic memory than is episodic remembering, consistent with high levels of activity in the lateral temporal cortex for EFT

(Addis et al., 2007). During EFT, semantic knowledge may provide a "scaffold" from which episodic details can be searched and integrated (D'Argembeau & Mathy, 2011; Irish, Addis, Hodges, & Piguet, 2012a). Patients with semantic dementia, indeed, have impaired EFT in the face of preserved episodic remembering (Duval et al., 2012; Irish et al., 2012a, 2012b), and the EFT impairment relates to atrophy in the left inferior temporal gyrus and bilateral temporal poles, and with performance in semantic memory tests (Irish et al., 2012a). EFT, however, also requires cognitive abilities that go beyond episodic memory, semantic memory, and executive functions (Ward, 2016). First, EFT is typically communicated through language, and therefore requires narrative abilities (Gaesser et al., 2011; Hassabis & Maguire, 2009; Suddendorf & Corballis, 2007). Narrative abilities may be altered following MTL damage (Rosenbaum et al., 2009; Race, Keane, & Verfaellie, 2015; Zeman, Beschin, Dewar, & Della Sala, 2012), or in healthy aging (James, Burke, Austin, & Hulme, 1998). Yet, Race and colleagues have shown that, in amnesic patients with MTL lesions, impaired EFT can withstand a preserved ability to describe (visually presented) scenes (Race et al., 2011; Race, Keane, & Verfaellie, 2013; but see Zeman et al., 2013), suggesting that MTL patients' EFT deficits are unlikely to be due to problems narrating constructed events.

Patients with lesions to the vmPFC may also show a deficit in episodic remembering and future thinking. Previous studies have shown that vmPFC patients produced past and future events characterized by few internal (episodic) details and reduced richness and spatial coherence than healthy and brain-damaged controls when they simulate extended mental events (Bertossi, Aleo, et al., 2016; Bertossi, Tesini, et al., 2016; but see Kurczek et al., 2015). Interestingly, vmPFC patients' event construction deficit extends to atemporal, fictitious events (Bertossi, Aleo, et al., 2016) and to events happening to other people (Bertossi, Tesini, et al., 2016), suggesting that vmPFC critically supports core constructive processes needed to simulate any complex event, regardless of temporal focus or self-reference.

The present study

In the present study, we investigated whether vmPFC patients have impaired EFT, and the nature of their impairment. In particular, we explored whether nonepisodic mechanisms, namely, narrative and working memory abilities, played a role in previous findings of event construction deficits in vmPFC patients (Bertossi, Tesini, et al., 2016; Bertossi, Aleo, et al., 2016; but see Kurczek et al., 2015). Previous studies have shown that vmPFC patients have normal discourse cohesion and coherence (Kurczek & Duff, 2011), and are normally able to recount fairy tales and Bible stories (Gilboa et al., 2006), suggesting preserved narrative abilities. As such, one would expect to find EFT problems in vmPFC patients even while controlling for narrative construction abilities. However, so far none has assessed EFT and event description in vmPFC patients within the same experimental paradigm, and, therefore, the relation between EFT and narrative construction in vmPFC patients is still unclear.

In addition to narrative abilities, EFT requires to maintain active the constructed event in working memory while describing it. EFT and working memory are related in healthy individuals. For example, the number of internal details in EFT has been found to correlate with individuals' digit span backward (Addis et al., 2008), and with performance in the listening span test, a task requiring to listen to a list of sentences and recall the last word of each sentence in the list (Zavagnin, De Beni, Borella, & Carretti, 2015). Using four different working memory measures, (Hill & Emery, 2013) have shown that EFT specificity relates to working memory abilities. It is long known that the prefrontal cortex is involved in working memory (Shallice & Burgess, 1991; for a review, see Esposito & Postle, 2015), and regions in the medial prefrontal cortex are particularly active when the material to be held in working memory is social in nature (Meyer & Lieberman, 2012), as typically is the content of EFT (D'Argembeau et al., 2011). It is possible, therefore, that problems in working memory play a role in vmPFC patients' EFT impairment. Interestingly, in the study by Bertossi, Tesini, et al. (2016), five of the seven vmPFC patients had at least one aspect of working memory impaired, though the group average fell within the normal

limits. In contrast, patients tested by Kurczek et al. (2015) had relatively intact cognitive functioning. Thus, discrepancies between previous studies with regard to vmPFC patients' EFT impairment may relate to differences in patients' cognitive profile. Here, vmPFC patients and healthy participants imagined future events using pictures as cues (EFT condition), described pictures (description condition), or described pictures while maintaining them in working memory after an observation phase (working memory condition). If vmPFC patients' deficits in EFT could be attributed mainly to impairment of the episodic memory system, as we hypothesize, the reduction in episodic detail and specificity should be present in the EFT condition but not, or in a reduced form, in the description and working memory condition. Alternatively, if mechanisms other than memory contribute to EFT performance, we would expect parallel patterns across tasks.

Method

Participants

Participants included six patients with vmPFC damage (vmPFC patients) and 11 healthy controls (Table 8 displays demographic and clinical information). Patients were tested at the Centre for studies and research in Cognitive Neuroscience of the University of Bologna, Italy, in the context of a periodic clinical assessment. Healthy participants were recruited among patients' relatives or other volunteers. All participants were native Italian speakers. Patients and controls were matched in terms of age, $t = 0.49$, $p = .63$ and education, $t = -0.02$, $p = .98$. The vmPFC patients' lesions were the results of the rupture of an aneurysm of the anterior communicating artery in all cases. Lesions were bilateral, though often asymmetrically so (i.e., in 2 patients the lesion was larger in the left hemisphere, and in 4 patients in the right hemisphere; Figure 3). Included patients were in the stable phase of recovery (at least 3 year postmorbid), were not receiving psychoactive drugs, and had no other diagnosis likely to affect cognition or interfere with the participation in the study (e.g., significant psychiatric disease, alcohol abuse, history of cerebrovascular disease). As well, the healthy individuals were not taking psychoactive drugs, and were free of current or past

psychiatric or neurological illness as determined by history. Participants gave informed consent to take part in the study, according to the Declaration of Helsinki (International Committee of Medical Journal Editors, 1991) and the departmental ethical committee.

Lesion analysis

Patients' individual lesions, derived from the most recent MRI or computerized tomography images, were manually drawn by a neurologist, or by a trained psychologist and then verified by the same neurologist (both were not involved in the present study and blind to task performance), directly on each slice of the normalized T1- weighted template MRI scan from the Montreal Neurological Institute provided with the MRIcro software (Rorden & Brett, 2000) (see also Karnath, Fruhmann Berger, Küker, & Rorden, 2004; Moro et al., 2008; Tsuchida & Fellows, 2012). This template is approximately oriented to match Talairach space (Talairach & Tournoux, 1988) and is distributed with MRIcro. This manual procedure combines segmentation (identification of lesion boundaries) and registration (to a standard template) into a single step, with no additional transformation required (Kimberg, Coslett, & Schwartz, 2007). MRIcro software was used to estimate lesion volumes (in cubic centimeters [cc]) and to generate lesion overlap images. Figure 3 shows the extent and overlap of brain lesions in vmPFC patients. Brodmann's areas (BAs) mainly affected in the vmPFC group were areas BA 10 (including, in some cases, the frontal pole), BA 11, BA 24, BA 25, BA 32, with region of maximal overlap occurring in BA 11 (M = 22.55 cc, SD = 8.80), BA 10 (M = 14.14 cc, SD = 4.36), and BA 32 (M = 9.25 cc, SD = 2.76). Two patients also had minimal damage in BA 46 and BA 47, accounting for about 6% and 3% of patients' total lesion size, respectively. Excluding these patients from the analyses did not alter the pattern of results.

Neuropsychological assessment

Patients' general cognitive functioning was preserved, as indicated by the scores they obtained in the Raven standard matrices (Spinnler & Tognoni, 1987), which were within the normal range in all cases (equivalent score [ES] = 2.83; note that the ES ranges from 0 = impaired performance, and 1 = borderline performance, to 2-4 indicating normal performance; Capitani &

Laiacona, 1988), and comparable between vmPFC patients and healthy controls, t = -1.63, p = .12. The vmPFC patients also received a more extensive neuropsychological evaluation, aimed at specifying their cognitive profile further.

Table 9 portrays individual vmPFC patients' scores in standardized neuropsychological tests. The vmPFC patients reported normal scores in tests of verbal short-term memory (STM; Digit Span Forward subscale: ES = 3; Spinnler & Tognoni, 1987), spatial STM (Corsi test span: ES = 2.83, supra span test: ES = 3.17), and working memory (2-back task; false alarms: t = 37.5, omissions: t = 45.8, RTs: t = 42.8, cut-off = 30; Zimmermann & Fimm, 2002; Zoccolotti, Pizzamiglio, Pittau, & Galati, 1994). Long-term memory, as assessed with the Buschke–Fuld list-learning test (Buschke & Fuld, 1974; long term retrieval ES = 1.17) and a prose-passage recall test (ES = 1.5; Spinnler & Tognoni, 1987), was weak, but within the normal limits. Additionally, patients did not show spontaneous confabulation, based on clinical evidence, their behaviour in real life, and interviews with family members (Schnider, 2008). Many aspects of executive functioning were also preserved, including planning, as assessed with the Tower of London test (t = 44.67, cut-off = 30) (Culbertson & Zillmer, 2000), inhibition, as assessed with the Stroop test (mean number of errors = 0.91, cut-off > 7.5; Spinnler & Tognoni, 1987), and cognitive flexibility, as assessed with the Wisconsin Card Sorting Test (t for perseverative responses = 30.5, cut-off = 30; Heaton, Chelune, Talley, Kay, & Curtis, 2000). Verbal fluency was within the normal limits as well (phonemic fluency: ES = 2.17; semantic fluency: ES = 2.83).

Stimuli

Eleven coloured pictures (size: 640 x 480 pixels) were selected from the International Affective Picture System (Lang, Bradley, & Cuthbert, 2008). All pictures were positive in valence (M = 6.31, SD = 1.12), and depicted people engaged in activities to which both patients and controls could easily relate (see also Gaesser et al., 2011; e.g., enjoying a picnic, playing football, playing with kittens, taking a stroll, eating dinner, answering the phone, taking the sun, fishing, etc.). Nine pictures served as the experimental trials, and two were used during the explanation of

the task and the practice phases, respectively. For each participant, the assignment of the nine pictures to the three experimental conditions was randomized, as was the order of presentation of each picture within each condition.

Table 8. Participants' Demographic and Clinical Information.

Group	*N*	Age (years)	Education (years)	Sex	SRM
vmPFC patients	6	55.66 (2.75)	11.50 (1.11)	6 males	35.50 (3.08)
Healthy controls	11	54.09 (1.81)	11.54 (1.16)	10 males; 1 female	40.81 (1.74)

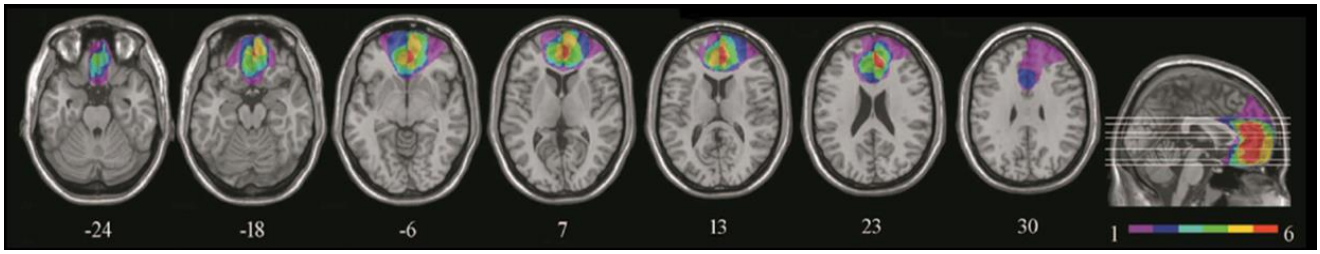
Note. vmPFC = ventromedial prefrontal cortex; SRM = standard Raven matrices; For SRM we report the mean uncorrected scores. The values in parentheses are standard errors of the mean.

Task

We used a task adapted from Gaesser et al. (2011). For each trial, participants either imagined an event using the picture as the general setting (3 trials; EFT condition), described details about the picture (3 trials; description condition), or described details about the picture after it had been removed from view following an observation phase (3 trials; working memory condition). In the EFT condition, participants imagined events that may happen to them in the next 2-3 years using the picture as the general setting. The picture remained on the screen until the end of the trial. Imagined experiences did not need to strictly involve the elements presented in the picture, so that participants would successfully generate an event. Imagined experiences had to be specific in time and place, novel (not been previously experienced by the participant), plausible (consistent with the participant's plans for the future), and last several minutes to hours, but not more than a day (see also Gaesser et al., 2011). In the description condition, participants had to describe the content of the picture, that is, the different people, objects, and environment in the picture (e.g., What are the people doing? What do they look like? Where are they?; see also Gaesser et al., 2011). Participants were instructed to report only what was depicted in the picture, without embellishing. In the working memory condition, participants first observed a picture. When they indicated that they had explored it satisfactorily, it was removed from view, and participants had to describe its content, with the same instructions as in the description condition. Observation was self-paced, but generally

lasted less than a minute across groups (see below). We are aware that, given that the capacity of visual working memory is about three to four objects (Vogel, Woodman, & Luck, 2001), and we used relatively complex pictures as stimuli, performance in the working memory condition is, at least in some cases, likely reflective of anterograde memory (in addition to working memory) abilities. Despite not being process-pure, our working memory condition mirrors closely the naturalistic requirement of EFT in terms of having to describe a complex event one has in mind. Trials were blocked by condition to facilitate compliance with task instructions, and the order of the three conditions was counterbalanced across participants. In all conditions, participants recounted as many details as possible for 5 min, and a tag reminding them of the ongoing task was always displayed at the bottom of the screen. The examiner (author V.C.), who was blind to the hypotheses of the study, used general prompts when necessary to clarify the instructions, solicit further detail, or make sure participants felt like anything else could be added, but could not introduce any concept not mentioned by the participant. Across conditions, after participants had recounted the scenario they were imagining/perceiving, they additionally rated: (a) how detailed was the future event imagined/the picture seen (detailedness: 1 = Not detailed at all; 4 = Very detailed), (b) the intensity of the emotion felt while imagining the future event/seeing the picture (emotionality: 1 = low emotion; 4 = high emotion), and (c) how difficult was the task (difficulty: 1 = Very easy; 4 = Very difficult). Participants' reports were recorded and transcribed for later scoring.

Figure 3. extent and overlap of brain lesions. The figure represents vmPFC patients' lesions projected on the same seven axial slices and on sagittal view of the standard Montreal Neurological Institute brain. The white horizontal lines on the sagittal view are the positions of the axial slices, and the white numbers under the axial views are the z coordinates of each slice. The color bar indicates the number of overlapping lesions. Maximal overlap occurs in BAs 11, 10, and 32. The left hemisphere is on the left side. See the online article for the colour version of this figure.



Procedure

The majority of testing took place at the Centre for studies and research in Cognitive Neuroscience of the University of Bologna. In some instances, participants were tested in their homes due to transportation difficulties. In such instances, a quiet area free from distractions or interruptions was used for testing. In all cases, the participant and the experimenter were the two only people present. The experimental task took about an hour to complete. The neuropsychological assessment took place in separate sessions.

Table 9. Neuropsychological Test Scores for vmPFC Patients.

Test	P1	P2	P3	P4	P5	P6	Mean
Raven matrices	34	33	30	42	27	47	35.50
Digit span forward	6	7	3*	5	5	7	5.50
Corsi span forward	6	6	3*	5	4	7	5.17
Corsi supra span	27.8	28.5	12.6	22.5	12.7	28.7	22.1
2-back WM task							
False alarms	0	8	70*	2	15*	3	16.33
Omissions	4	1	1	1	5	1	2.17
Reaction times	1,139	686	485	527	1,021	773	772
Tower of London test							
Total move score	44	44	62	3	69	31	42.17
Phonemic fluency	33	26	23	24	28	20	25.67
Semantic fluency	39	45	36	35	22	55	38.67
Stroop test errors	1	0	1	0	3	.5	.91
WCST perseverative errors	32	64*	38	41	92*	76*	57.17
Buschke-Fuld test LTM	103	126	108	21*	60	56*	79
Prose recall test	15	14	6.7	3.5*	3.3*	7	8.25

Note. vmPFC = ventromedial prefrontal cortex; WM = working memory; WCST = Wisconsin Card Sorting Test; LTM = long-term memory retrieval score. We report uncorrected scores, and asterisks indicate performance below the normal limits according to normative data (see the Neuropsychological Assessment section).

Scoring

Participants' records were scored using the Autobiographical Interview protocol developed by Levine, Svoboda, Hay, Winocur, & Moscovitch (2002) and adapted following Gaesser et al. (2011). For each trial, the central event was identified and, if more than one event was mentioned, the event described in more detail was considered the main event. Each event was divided into distinct details (unique bits of information), and these details were classified as internal (episodic details) or external (semantic information, repetitions, and information not specific to the main event). Verbatim descriptions of the items part of the picture were scored as external details for the EFT condition, so that only truly imagined events counted as internal details in EFT trials. In

contrast, such verbatim descriptions scored as internal details for both the description and working memory condition. Inferences about the picture (e.g., speculations, interpretations of peoples' actions) were scored as external details in both the description and working memory condition. For the working memory condition, elements that were not present in the picture, or were reported in the wrong position, counted as external details. Two raters scored the transcripts independently. A main rater (blind to the hypotheses of the study) scored all reports, and a second rater scored 62% of the reports. Interrater reliability for internal and external details between the two raters was assessed with intraclass correlation (McGraw & Wong, 1996), which indicated high agreement between the two scorers (Cronbach's alpha = .98 and 0.89 for internal and external details, respectively).

Statistical analyses

For each event/description, internal and external details were tallied. For each condition, the details were averaged across the three imagined/descripted events, separately for internal and external categories. Statistical analyses on the number of details generated were run using a 2 (group: healthy controls, vmPFC patients) x 3 (condition: EFT, description, working memory) x 2 (detail: internal, external) analysis of variance (ANOVA), and Fisher tests as post hoc comparisons. Analysis of covariance (ANCOVA) was used to investigate, and control for, the effect of description and working memory performance on EFT. Given the small sample size, the main results were confirmed using more robust, nonparametric Mann–Whitney tests. Subjective ratings, which were nonnormally distributed (Kolmogorov–Smirnov $d > 0.37$, $p < .05$), were analyzed using Mann–Whitney tests as well. In addition to group analyses, we performed individual modified *t* tests based on Crawford and Garthwaite's (2002) method for comparing single cases with small control samples, to analyze individual patients' EFT performance and relate it to their cognitive profile. Unless noted otherwise, the level of significance was set at $p < .05$, two-tailed. We report Cohen's *d* and partial η^2 as measures of effect size.

Results

The results obtained by vmPFC patients with lesions mainly in the left hemisphere were comparable to those obtained by vmPFC patients with lesions mainly in right hemisphere (see the Lesion Analysis section; Mann–Whitney tests: $z > -1.39$, $p > .16$ in all cases). Therefore, for clarity, we present the results collapsed across the whole group of vmPFC patients.

Ratings

Subjective ratings of detail, emotionality, and difficulty were not significantly different between vmPFC patients and healthy controls ($z > -1.66$, $p > .07$ in all cases).

Details

Figure 4 shows the number of internal and external details generated by vmPFC patients and controls in the EFT, description, and working memory conditions, and Table 10 shows representative excerpts of participants' reports across the different conditions. An ANOVA on the number of details generated with group, condition, and detail as factors showed a significant main effect of group ($F(1,15) = 11.25$, $p = .004$, partial $\eta^2 = 0.43$) and a significant main effect of detail ($F(1,15) = 10.60$, $p = .005$, partial $\eta^2 = 0.41$), which were qualified by a significant Group x Detail interaction ($F(1, 15) = 4.68$, $p = .04$, partial $\eta^2 = 0.24$). Post hoc tests showed that vmPFC patients produced fewer internal details than controls across conditions ($p = .0004$, $d = 1.50$), whereas the number of external details did not differ significantly between groups ($p = .24$, $d = 1.37$). Group differences in internal details were confirmed using nonparametric Mann–Whitney tests (EFT condition: $z=-3.17$, $p = .001$; description condition: $z=-2.01$, $p = .04$; working memory condition: $z =-3.01$, $p = .003$). A main effect of Condition also emerged ($F(2,30) = 4.12$, $p = .02$, partial $\eta^2 =0.21$), qualified by a Condition x Detail interaction ($F(2,30) = 19.41$, $p = .000004$, partial $\eta^2 =0.56$): both groups provided more internal details in the description (29.02, $p < .000001$, $d = 1.08$) and working memory condition (24.68, $p = .00005$, $d = 1.00$) than in the EFT condition (13.88), and more external details in the EFT than in the working memory condition (15.33 vs. 7.86, $p = .002$, d

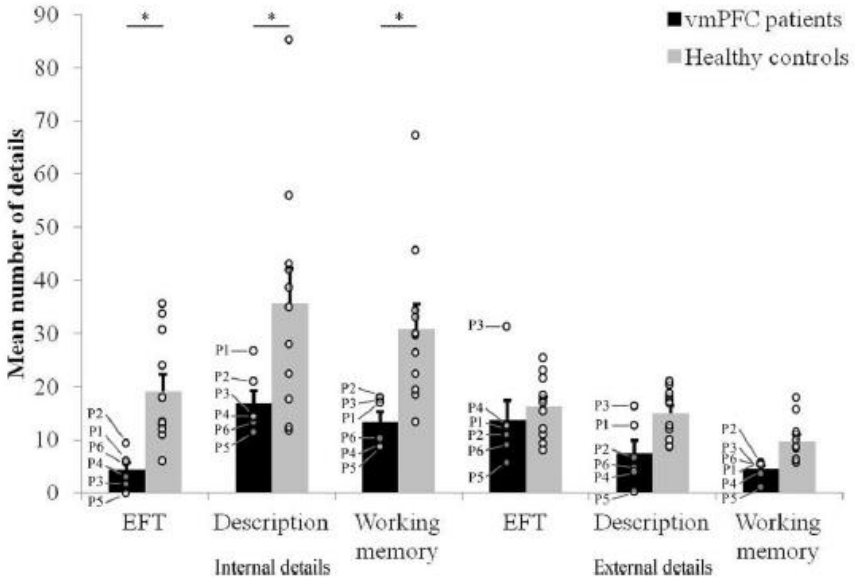
= 1.06). No other significant post hoc comparison emerged ($p > .06$, $d < 0.82$). No other main effects or interactions in the ANOVA were significant (all p values >0.53, partial η^2 <0.05).

These findings show that vmPFC patients show an impairment not only in imagining events, but also in describing events, be these perceived or held in working memory (see Figure 4). It is important to note here that vmPFC patients spent as much time as controls examining the pictures to be held in working memory (0.71 vs. 0.85 min, $t = -0.52$, $p = .61$, $d = 0.26$), to describe pictures (description condition: 2.25 vs. 3.11 min, $t=-1.64$, $p = .12$, $d = 0.83$; working memory condition: 1.43 vs. 2.24 min, $t = -1.59$, $p = .13$, $d = 0.81$), and to recount imagined future events (3.54 vs. 3.29 min, $t = 0.44$, $p = .66$, $d = 0.22$), suggesting they were normally engaged in the tasks, and not superficial or hurried. We then investigated whether group differences in EFT were fully explained by participants' performance in the description and working memory conditions, by adding the number of internal and external details produced in the description and working memory conditions as covariates in an ANCOVA on the number of details generated during EFT with group, condition, and detail as factors. We examined the collinearity statistics of the predictor variables and found that tolerance was >0.25 and the variance inflation factor (VIF) was <3.90 in all cases, indicating no evidence of a multicollinearity problem. The ANCOVA still showed a significant Detail x Group interaction ($F(1,11) = 6.44$, $p = .02$, partial $\eta^2 = 0.37$), with vmPFC patients providing fewer internal details (4.28 vs. 19.12, $p = .0004$, $d = 1.50$) but a similar number of external details than healthy controls ($p = .47$, $d = 1.37$). Thus, even though vmPFC patients had problems describing events, be those present or held in working memory, these problems did not account fully for their EFT impairment.

We also calculated the proportion of internal to total (internal + external) details as an additional index of EFT performance, independent of verbosity (Figure 5). An ANOVA on the proportion of internal-to-total details with group and condition as factors revealed a main effect of condition ($F(2,30) = 46.05$, $p < .000001$, partial $\eta^2 = 0.75$), qualified by a Group x Condition interaction ($F(2,30) = 10.52$, $p = .0003$, partial $\eta^2 = 0.41$). Fisher post hoc tests showed that the

proportion of internal-to-total details was lower in vmPFC patients than in healthy controls in the EFT condition (0.23 vs. 0.53, p = .00002, d = 2.10), but not in the description (0.72 vs. 0.67, p = .37, d = 0.36) or working memory condition (0.74 vs. 0.74, p = .98, d = 0). Mann–Whitney tests confirmed that the proportion of internal to total details was lower in vmPFC patients than in healthy controls in the EFT condition (z = -2.61, p = .009), but not in the description and WM conditions (p > .42 in both cases). Thus, vmPFC damage reduced the specificity of imagined future events, not of all events described.

Figure 4. Mean number of internal and external details by participant, group, and condition. EFT episodic future thinking. Bars represent standard errors of the mean. Circles indicate performance of individual participants, and P1, P2, . . ., P6 denote individual patients. * p < .05.



EFT and neuropsychological profile

We explored whether EFT performance was related to vmPFC patients' neuropsychological profile. First, individual Crawford and Garthwaite's (2002) t tests on the proportion of internal-tototal details generated during EFT revealed that patient P3 (t = -3.83, p = .003), patient P4 (t = -2.71, p = .02), and patient P5 (t = -4.23, p = .002) generated significantly less specific future events compared to healthy controls, whereas performance of the other three vmPFC patients fell within the normal limits (p > .18 in all cases), despite being generally lower than healthy controls' mean performance (see Figure 5). In light of the role of episodic memory, semantic memory, and

executive functions in EFT, we expected that the three vmPFC patients with more severely impaired EFT would be more compromised in these functions than the three vmPFC patients with EFT within the normal limits. Mann–Whitney tests revealed that vmPFC patients who generated an abnormally low proportion of internal-to-total details had lower scores in tests of long-term memory (prose recall, spatial supra span test), STM (digit span forward, Corsi test), and semantic fluency than vmPFC patients who generated a proportion of internal-to-total details within the normal limits ($z > 1.96$, $p < .049$, one-tailed, in all cases; see Table 8). Group differences in other neuropsychological tests were not significant ($p > .26$ in all cases).

Figure 5. Mean proportion of internal-to-total details by participant group and condition. EFT = episodic future thinking. Bars represent standard errors of the mean. Circles indicate performance of individual participants, and P1, P2, . . ., P6 denote individual patients. * $p < .05$.

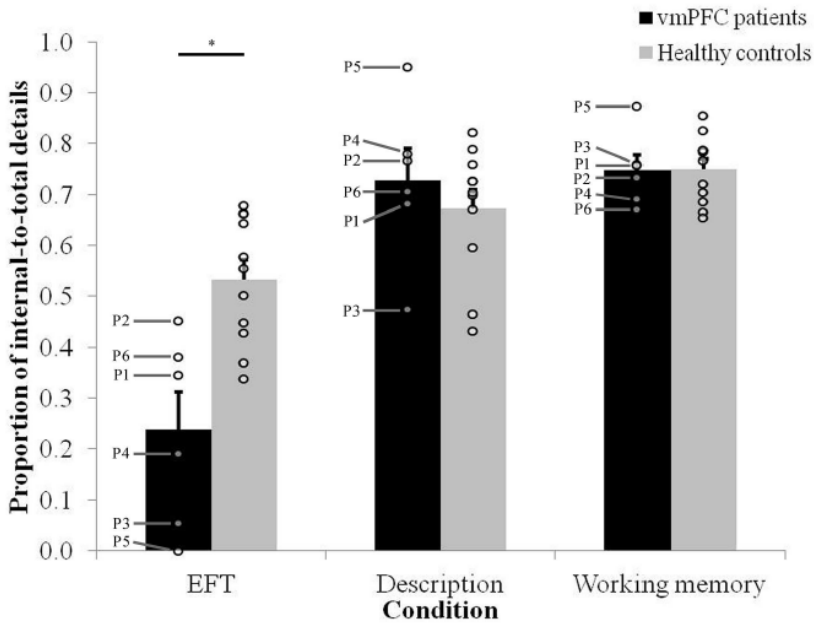


Table 10. Example reports generated in the EFT, Description, and Description from Working Memory conditions by a vmPFC patient (P2) and a healthy control subject.

vmPFC patient	Healthy control
Future condition—Picture: a man sat at a dinner table	
P2 (Age: 45, Education: 14) I imagine myself in two or three years, I will be drinking a glass of good red wine at my friends' house, talking about politics. And even if I quit smoking after the aneurysm, in January six years will be passed since then already, so . . . I can see myself, with a wall mirror behind my back, which reflects a window on my side. I see a teapot, an ashtray, and some old pictures. All of this actually reminds me very much of my uncle (Italian surname)'s house. He was my grandfather's brother, who passed away ten years ago. Enough. [*Would you like to add something?*] No.	Control 1 (Age: 47, Education: 13) In three years, in 2017, I would like to start singing again after I gave up. And I will ask myself: "Who can I ask for a job?" I will dig into my past, and I will tell to myself: "I will ask Piero, (female name)'s husband." Who knows if he has aged . . . I will ask where he lives now. "He always lives in (Italian town)"—somebody who used to go to the dance halls with us will tell me. This person will also tell me that Piero no longer has his own orchestra. And I will ask: "What about his wife?" "I don't know about her"—he'll say—"but you should check." Then, I will go to Piero's house. It is an old house with very old furniture. I will find him changed a lot. He does not have his beard anymore, and he will wear glasses. He used to have white hair, but he now dyes his hair. I will say: "Who are you?!" "I'm Piero." "But you look even younger than when we played ballroom music together!" "Come on, sit down"—he' ll say. In the house there was a cupboard with many pictures: his grandmother, uncles, brothers, cousins. Moreover, there were bonbonnieres. The classic small cabinet with porcelains . . . The house was the same as in 1998 when I left him. He is a wine lover. He will ask me to sit at the table, and he will have his typical cigarette, unavoidable for Piero, and the conversation will start. I will ask: "Where could I start to sing?" And he'll say: "You are not in the loop anymore, you can't join the orchestra again. However you could think to be in charge of the audio mixing, because you know how to work with sounds very well. I may ask (Italian surname), no wait, his son, because sadly he is dead." He will give me his address in (Italian city). After drinking, he will give me a long hug, and tell me: "Good luck. I hope you will be able to start singing again, but for now you should be happy with being back as an audio mixer technician." [*Would you like to add something?*] No.
Description condition—Picture: two women having a stroll	
P2 There are two women going up a hill with two trolleybuses following them closely. An uphill road. Also, this looks like a cold place because the women wear heavy clothes. There is stuff hung under the sun. The two trolleybuses follow the tracks, and the pilot is not visible in any of them. Actually, one trolleybus is going up and the other is going down, so probably they have recently met. It is possible to see a mountain landscape, with air-conditioners on the top, some heat pumps, clearly visible. There is a yellow and orange house, a plant. Enough. [*Would you like to add something?*] No.	Control 2 (Age: 54, Education: 8) I can see an American setting with some old colored houses, and with many balconies and many air-conditioners. There are clothes hung up. It is quite rustic a road, I would say rural. There is a trolleybus that looks like going up, if I'm not wrong. There are two ladies who talk and walk, and a car parked in the alley, a van, and a lady with two suitcases. There are many cables suspended in the air, it is stunning how many they are. There seems to be a market at the bottom. I see some vans. The road is made of stones and it is old. I see many entrances of buildings, too many, about one every meter. There is a house at the bottom, yellow and red, maybe these are actually two houses, owned by different people. There is a small roof. Stop. [*Would you like to add something?*] There are a lot of things, there are plants hung up, I don't know if there is a shop or something similar, I see air-conditioners, and clothes hung up. This seems like a secondary road, not a main one, but it is very characteristic anyway.
Working memory condition—Picture: a secretary answering the phone in her office	
P2 The picture represented a lady speaking at the telephone, which she held with her left hand. Yes. Whereas with her right hand she was playing with something, I don't know what. She was playing with her fingers. And there was a computer, 80s' model. Behind her, there was a plant on the right, I mean my right. Behind her, on the left, there was a cabinet. The lady dressed in a cheap way. She had a white blouse with a beige jacket. She did not wear the glasses. Enough. [*Would you like to add something?*] No.	Control 3 (Age: 41, Education: 14) We are in an office, I would say in the 80s. There is a woman talking on the phone, and, behind, a light blue wall with, on the right, a shelf, and a grey cabinet. It is possible to glimpse two large drawers. On the left, I'd say that there is the screen of an 80s computer, a computer with a cathodic tube. Underneath, there is another part of the computer, and the keyboard is also visible. There is a desk, the woman sat at a desk. On the desk there is a white notebook, and it is possible to glimpse a pair of glasses. She has her hands on the desk, and the hands are slightly contracted. The telephone is from the 80s as well, it is possible to see it clearly. She has her index finger on the receiver, and three fingers wrapping the receiver. She is speaking, she has her eyes half-closed, hair tied back from the face, dark hair, almost black, and long. She has a very ugly jacket, with shoulder pads, and a white blouse. On the left there is a plant, I think it is a ficus benjamin, but it is in the shadow because it is not possible to see the color of the leaves clearly. The plant, she's calling . . . She has her eyes closed . . . what else . . . she has a light make-up, and it is possible to see from her mouth that she is going to talk. Down, on the right, there is this beige telephone and the cable is twisted, wrinkled, whitish. That's it. [*Would you like to add something?]* I said the glasses . . . and the keyboard too. No, that's all.

Note. EFT = episodic future thinking; vmPFC = ventromedial prefrontal cortex; Parentheses are used to indicate information added to clarify the significance of some detail, or when omitting information that may help identify participants. Brackets are used to highlight the experimenter's statements (in italics).

Discussion

We investigated the role that nonepisodic abilities, such as narrative construction and working memory maintenance, play on vmPFC patients' ability to imagine specific future events, by having vmPFC patients and healthy controls imagine specific personal future events (EFT) or describe pictures they were perceiving or holding in working memory. The results indicate that vmPFC patients generated fewer internal details during EFT but a normal number of external details. In the present study, unlike previous ones (Bertossi, Aleo, et al., 2016; Bertossi, Tesini, et al., 2016; Kurczek et al., 2015), we used pictures (instead of words) as cues for EFT, in order to match the nature of the cues between the EFT and the description conditions. Pictorial (compared with verbal) cues have been found more effective at eliciting specific autobiographical memories (Ridout, Dritschel, Matthews, & O'Carroll, 2016), which could have facilitated EFT in our patients. Yet, we confirmed that vmPFC patients are impaired in the episodic simulation of future events (see also Bertossi, Aleo, et al., 2016; Bertossi, Tesini, et al., 2016). The vmPFC patients' EFT deficit aligns with extensive fMRI evidence of vmPFC engagement during EFT (Okuda et al., 2003; Addis et al., 2007; Hassabis, Kumaran, & Maguire, 2007; D'Argembeau et al., 2010).

Our findings, however, also highlight a deficit in nonepisodic abilities that likely contribute to, though do not completely explain, vmPFC patients' EFT deficit. The vmPFC patients, indeed, produced less detailed descriptions of pictures compared to healthy controls, be these in view or held in working memory, often conveying only the general sense of what the pictures portrayed, not the fine details. It is worth noting that a deficit in describing pictures is not present in patients with hippocampal amnesia (Race et al., 2011, Race et al., 2013), but may occur in the presence of extra-MTL damage (Zeman et al., 2013). As Zeman et al. (2013) noted, this deficit may be due to problems in executive functions, which were weak in our patients. Prefrontal cortex is an important source of top-down modulation of visual processing (Desimone & Duncan, 1995). In particular, vmPFC is active during visual search (Pantazatos, Yanagihara, Zhang, Meitzler, & Hirsch, 2012), and vmPFC patients have impaired visual scanning strategies (Wolf, Philippi, Motzkin, Baskaya, &

Koenigs, 2014). Thus, vmPFC patients may fail to detect all of the objects in a scene. Indeed, vmPFC is active, along with the hippocampus, during perception (not only construction) of scenes (Zeidman, Mullally, & Maguire, 2015). The vmPFC patients also have problems integrating elementary features into global percepts, especially when perceptual integration relies heavily on the top-down activation of a search template (Ciaramelli, Leo, Del Viva, Burr, & Ladavas, 2007). Setting up a global representation of a scene (i.e., schema; Biederman, 1981) supports, in turn, the detection of additional individual objects (Hassabis & Maguire, 2009). Thus, vmPFC damage may have deprived patients from top-down guidance of perception, further hindering the identification of picture details (Barceló, Suwazono, & Knight, 2000).

Whether due to poor search/detection of perceptual details, or merely vmPFC patients' narrative style (which may not be entirely captured by the number of internal and external details produced), impaired descriptive abilities do not fully account for vmPFC patients' EFT impairment. As well, vmPFC patients' EFT impairment does not seem to be the reflection of a general problem in fluency. When we control EFT performance for individuals' verbosity by focusing on the proportion of internal-to-total details, indeed, vmPFC patients still evinced lower EFT scores than controls, whereas group differences in description and working memory vanished. Thus, while differences in descriptive abilities between vmPFC patients and healthy controls likely reflect differences in the overall amount of information reported, group differences in EFT highlight qualitative differences in event construction between vmPFC patients and controls, with the former disproportionately impaired in the generation of episodic details.

One possibility is that vmPFC patients had problems accessing personal future events specific in time and place. The frontopolar cortex, which was damaged in our patients, is related to prospective thinking (Burgess et al., 2001; D'Argembeau, Stawarczyk, Majerus, Collette, Van der Linden, Feyers, et al., 2010), and is preferentially engaged by construction of future (compared with past) events (Addis et al., 2007). Alternatively, vmPFC may mediate integrative processes needed to elaborate specific future (as well as past) events (see also Bertossi, Aleo, et al., 2016; Bertossi,

Tesini, et al., 2016). The vmPFC is known to be critical for appropriate processing of schema-related information (Ghosh, Moscovitch, Melo Colella, & Gilboa, 2014), and represents abstract summaries of frequent events (Krueger, Barbey, & Grafman, 2009). During event construction, this region may help maintain a stable schematic knowledge of relevant events (e.g., the typical picnic) around which to construct a rich and contextualized event, using past experiences as a source of details (Benoit, Szpunar, & Schacter, 2014). Consistent with this hypothesis, performance in semantic, but not phonemic, fluency was lower in a subset of vmPFC patients who reported a particularly low proportion of internal-to-total details during EFT compared with patients whose performance fell within the normal range. These findings, again, argue against the idea that vmPFC patients' EFT problems reflect a general problem in fluency, and reinforce the hypothesis that patients may have problems activating and using semantic structures crucial for EFT (D'Argembeau & Mathy, 2011; Irish et al., 2012a).

The vmPFC patients with more severe EFT specificity problems were also those that scored poorly in short- and long-term memory tests. The "constructive simulation hypothesis" emphasizes the role of episodic memory in EFT (Schacter et al., 2012). Indeed, the same associative processes binding information in a laboratory prose-recall task may be necessary to collate individual episodic details into novel events. In fact, the discrepancy between impaired (Bertossi, Tesini, et al., 2016) and preserved (Kurczek et al., 2015) EFT in different groups of vmPFC patients may reflect, at least in part, differences in patients' mnestic abilities. Patients tested by Bertossi, Tesini, et al. (2016), who had impaired EFT, were also impaired in list-learning tasks, whereas patients tested by Kurczek et al. (2015) had preserved EFT as well as anterograde and retrograde memory. STM, too, has been found to support episodic binding (Bridge & Voss, 2015). The crucial question, now, concerns the nature of the memory processes mediated by vmPFC that serve both anterograde learning and EFT. Of relevance, although vmPFC patients may have weak working memory abilities (Bertossi & Ciaramelli, 2016; Bertossi, Tesini, et al., 2016), we have no evidence that vmPFC patients' EFT impairment depended on working memory deficits. Indeed, vmPFC patients

with versus without a severe EFT impairment did not differ in working memory performance. Moreover, vmPFC patients were not disproportionately impaired at describing pictures held in working memory versus in view, compared with healthy controls.

In summary, our results confirm that vmPFC have a deficit in EFT. Although vmPFC patients' event description performance appears to indicate that mechanisms other than episodic memory are also relevant to understanding their EFT impairment, such as narrative construction and working memory, these proved not to be the root of their impairment. Our work, therefore, encourages further inquiry of the specific subcomponents of the episodic memory system involved in EFT and of the role of vmPFC in event simulation.

Chapter 3.

The role of ventromedial prefrontal cortex and hippocampus in scene construction.

The previous study has left many questions open. First, study 2 shows that vmPFC patients are impaired not only in the construction of future events, but also in description of event pictures. Although we have demonstrated that the poor narrative skills do not completely explain vmPFC patients' EFT impairment, this finding leads to interrogate about the nature of the task used to assess event simulation and suggests the importance of investigating this ability using tasks that do not require narrative skills. In this chapter, studies 3 and 4 have this specific aim, to assess a core component of event simulation, namely the construction of single scenes, through tasks based on the use of scene pictures, and not requiring to verbally describe the constructed scenes.

Second, study 2 replicates previous findings that vmPFC patients are impaired at simulating mental events (Bertossi, Aleo, et al., 2016; Bertossi, Tesini, et al., 2016), an ability that requires explicit scene construction mechanisms. However, there is no evidence, so far, about the role of vmPFC in implicit, automatic, scene construction. Therefore, this issue will be directly investigated in study 3 of this chapter, while study 4 will examine the ability to process-as opposed to create- the constructive and semantic aspects of scenes.

Third, study 2 found that vmPFC patients are impaired at simulating future extended events. However, as anticipated, in a different study (Kurczek et al., 2015), vmPFC patients have been found capable to describe in detail single snapshots of scenes taken from pre-selected events, and their performance strikingly differed from that of MTL patients, who were instead impaired even in the simulation of these single snapshots (Kurczek et al., 2015). This finding leads to think that a crucial difference between these patient populations lies in the distinct roles that vmPFC and hippocampus play in the scene construction process, with vmPFC involved in constructing extended events, and the hippocampus implicated in building even single scenes. In the following studies

focused on scene construction and processing, therefore, we will compare the performance of vmPFC patients and hippocampal patients, to begin to shed light on the different contribution played by these brain regions during scene construction.

Study 3. Boundary extension is attenuated in patients with ventromedial prefrontal cortex damage.

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(De Luca F, McCormick C, Mullally SL, Intraub H, Maguire EA, Ciaramelli E. 2018. 108:1-12. *Cortex*)

Introduction

For most of us, if we close our eyes we can construct vivid mental scenes and events that help us to remember the past, envision the future and create fictitious scenarios. Neuroimaging and neuropsychological evidence has pinpointed several key brain regions that seem to support these functions, including the ventromedial prefrontal cortex (vmPFC) and hippocampus (Svoboda, McKinnon, & Levine, 2006; Addis, Wong, & Schacter, 2007; Hassabis, Kumaran, Vann, & Maguire, 2007; Lah & Miller, 2008; Race, Keane, & Mieke Verfaellie, 2011; Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016; Bertossi, Tesini, Cappelli, & Ciaramelli, 2016). However, the separate contributions of vmPFC and hippocampus are not well understood. One way to try and dissociate the roles of these two brain regions is to administer tasks that have been associated with one brain structure to patients with damage to the other brain structure. Emerging evidence suggests that the hippocampus is necessary for constructing mental models of spatially-coherent scenes in which details can be bound in order to be re- or pre-experienced (Maguire & Mullally, 2013; Clark & Maguire, 2016; Zeidman & Maguire, 2016; McCormick, Ciaramelli, De Luca, & Maguire, 2017).

In this regard, an especially intriguing scene construction phenomenon is “boundary extension” (BE) (Intraub & Richardson, 1989; Intraub, 2012). BE occurs when individuals who are viewing scenes automatically imagine what might be beyond the view, and consequently later misremember having seen a greater expanse of the scene. BE is a powerful psychological

phenomenon that has been replicated in many healthy populations, including adults (Intraub & Richardson, 1989; Intraub, Bender, & Mangels, 1992; Intraub, Gottesman, & Bills, 1998; Chadwick, Mullally, & Maguire, 2013), children (Seamon, Schlegel, Hiester, Landau, & Blumenthal, 2002; Kreindel & Intraub, 2017), babies (Quinn & Intraub, 2007), and also cohorts with developmental disorders (Spanò, Intraub, & Edgin, 2017). What makes BE so intriguing is that healthy participants tend to make robust and confident memory errors despite seeing the original scenes just a few milliseconds beforehand. Therefore, BE provides a unique window into the implicit, automatic and fast process of internal scene construction.

Patients with bilateral hippocampal damage, who have impaired scene construction ability, show attenuated BE, leading to paradoxically better memory performance compared to control participants despite their amnesia (Mullally, Intraub, & Maguire, 2012). This is because when processing the scenes, the patients do so without using scene construction to extrapolate beyond the scene boundaries. When BE was examined using functional magnetic resonance imaging (fMRI), the importance of the hippocampus was further underlined (Chadwick et al., 2013; see also Park, Intraub, Yi, Widders, & Chun, 2007). Interestingly, effective connectivity analyses during BE showed that the hippocampus influenced activity in the visual-perceptual cortices rather than vice versa. This finding highlights one of the pathways underpinning this top-down process.

Whereas the previous fMRI study did not reveal any prefrontal cortex activation, the vmPFC has recently been implicated in top-down initiation of hippocampal processes (Garrido, Barnes, Kumaran, Maguire, & Dolan, 2015; for a review see (McCormick, Ciaramelli, et al., 2018); Moscovitch, Cabeza, Winocur, & Nadel, 2016). In addition, vmPFC-damaged patients are impaired at imagining future and fictitious events compared to control groups, and rate their constructed experiences as lacking spatial coherence (Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016). Together, these findings suggest that the vmPFC plays a role in mental scene construction, at least for tasks that are explicit and involve introspection.

The question we address here is whether vmPFC is equally involved in the fast, implicit and automatic process of BE. We investigated BE in patients with vmPFC lesions and also control patients with cortical lesions that did not involve the vmPFC. In addition, we contrasted their performance with the hippocampal patients described by Mullally et al. (2012). If vmPFC is necessary for scene construction, patients with vmPFC damage should show reduced BE compared to healthy and brain-damaged controls, similar to hippocampal-damaged patients. This would confirm the role of vmPFC in scene construction using a paradigm that probes construction implicitly, and in relation to single scenes. Importantly, the BE task allows to assess scene construction without relying on language and narrative skills, which are known to be poor in vmPFC patients, as shown in the study 2 (Bertossi et al., 2017). Therefore, a BE reduction would further confirm that the role of vmPFC in scene construction is independent from other mechanisms, as narrative construction. An additional 'scene probe' task allowed us to interrogate scene construction further in terms of perceptual, emotional, and spatial details, providing insight into the nature of the impairment associated with damage to the vmPFC or the hippocampus.

Methods

Participants

Twenty-five patients took part in the experiment. Eight patients had vmPFC damage (vmPFC patients; all males, mean age = 59.25 years, range = 46-72; see Table 11 for demographic and clinical information), and ten 'control' patients had brain damage that did not involve vmPFC or the hippocampus (control patients; seven males, mean age = 59.30 years, range = 45–67 years; Table 11). We also considered data from seven patients who had hippocampal damage (hippocampal patients; four males, mean age = 41.43 years, range = 32–63 years). vmPFC and control patients were Italian and were recruited at the Centre for Studies and Research in Cognitive Neuroscience, Cesena, Italy. Hippocampal patients were British, and were tested at the Wellcome Centre for Human Neuroimaging, University College London, UK. The background details of the

hippocampal patients and their scores on the BE tasks have already been reported in Mullally et al. (2012) (for convenience, background details are summarized in Supplementary Materials Table S1). Our main interest here was in the new data relating to performance of the vmPFC and control patients. We reprise relevant data from the hippocampal patients to afford direct comparisons with the vmPFC and control patients as an interesting secondary analysis.

Brain damage in vmPFC patients was bilateral in all cases, and the result of the rupture of an aneurysm of the anterior communicating artery (ACoA). In control patients, brain damage (left hemisphere: five cases; right hemisphere: five cases) was due to stroke (six cases), arteriovenous malformations (two cases), or tumor (two cases). Lesion sites in control patients included the occipital cortex and occipital-temporal area, and lateral aspects of the temporal and prefrontal cortex (see Supplementary Figure S1). The hippocampal-damaged patients' lesions were focal and also bilateral (Supplementary Materials Table S1; Figure S2; full details in Mullally et al., 2012). All patients were in a stable phase of recovery (at least 3 months post-lesion) and had no other diagnoses likely to affect cognition or interfere with participation in the study (e.g., significant psychiatric disease, alcohol abuse, history of cerebrovascular disease).

Ten Italian healthy individuals (vmPFC healthy controls; all males; mean age = 56.50 years, range = 44-63; see Table 11) were matched to the vmPFC and control patients on age ($F_{(2,25)} = 0.41$, $p = 0.67$), education ($F_{(2,25)} = 0.22$, $p = 0.80$), and gender balance (vmPFC: $\chi^2 = 0.00$, $p = 1.00$; control patients: $\chi^2 = 1.09$, $p = 0.30$). The hippocampal patients were generally younger than the vmPFC and control patients ($F_{(2,22)} = 9.77$, $p = 0.001$), and so were matched with twelve British healthy individuals (eight males, mean age = 42.67 years, range = 32–63; Supplementary Materials Table S1; see Mullally et al., 2012) on age ($U = 34$, $Z = -0.68$, $p = 0.496$), gender balance ($\chi^2 = 0.17$, $p = 0.68$), and IQ ($U = 22.5$, $Z = -1.66$, $p = 0.097$). Healthy control participants were not taking psychoactive drugs and were free of current or past psychiatric or neurological illness as determined by history. These sample sizes were chosen based on the previous neuropsychological study that examined BE (Mullally et al., 2012). Participants gave informed consent in accordance

with the Bioethical Committee of the University of Bologna, the CEIIAV Ethical Committee of Emilia Romagna Regional Health Service, and the National Research Ethics Committee (London, Queen Square, UK), and in line with the Declaration of Helsinki (International Committee of Medical Journal Editors, 1991).

Table 11. Demographic and clinical data of vmPFC patients, control patients, and vmPFC healthy controls.

	N	Gender	Age (years)	Edu (years)	SPM	Phonemic fluency	Semantic fluency	Digit span	Corsi test	Prose recall	ROCF copy	ROCF recall
vmPFC patients	8	8 M	59.25 (8.60)	9.88 (3.04)	28.84 (4.35)	24.75 (9.39)	38.25 (13.60)	5.50 (0.79)	4.48 (0.82)	8.27 (4.09)	31.28 (5.05)	13.63 (5.54)
Control patients	10	7 M, 3 F	59.30 (8.81)	9.50 (3.14)	24.78 (7.96)	32.00 (7.60)	48.40 (11.36)	5.43 (0.92)	4.03 (1.23)	11.75 (2.36)	29.22 (8.25)	13.08 (8.65)
vmPFC healthy controls	10	10 M	56.50 (5.70)	9.00 (2.11)	-	-	-	-	-	-	-	-

Notes. vmPFC = ventromedial prefrontal cortex; M = male; F = female; Edu = education; SPM = Ravens Standard Progressive Matrices; ROCF = Rey-Osterrieth Complex Figure. We report mean corrected scores (see Spinnler & Tognoni, 1987 for normative data), in all cases within the normal limits, and the standard deviation of the mean in parentheses.

Neuropsychological profile

Table 11 shows the vmPFC and control patients' neuropsychological profiles. In general the patients' cognitive functioning was preserved, as indicated by their scores on the Raven Standard Progressive Matrices (see Spinnler and Tognoni, 1987, for normative data) and verbal fluency (Spinnler and Tognoni, 1987), which were within the normal range in both groups. vmPFC and control patients also had intact verbal and spatial short-term memory, as assessed with the digit span and Corsi tests (Spinnler and Tognoni, 1987) and verbal and spatial long-term memory, as assessed with prose recall and recall of the Rey-Osterrieth complex figure (Spinnler and Tognoni, 1987). The copy of the Rey-Osterrieth complex figure was also normal (Spinnler and Tognoni, 1987). Direct comparison of the vmPFC patients and control patients showed comparable scores in the above neuropsychological tests ($p > 0.09$ in all cases) with the exception of prose recall, which was poorer in vmPFC compared to control patients ($t = -2.18$, $p = 0.045$). In some cases, control patients with posterior lesions had visual field deficits, including hemianopia (in six cases) and quadrantopia (in

one case). In these patients, however, detection of visual stimuli in standardized tests was not impaired when eye movements were allowed, and visual search performance was within the normal limits (see Supplementary Table S2). We therefore assumed they would be able to perform the BE task (see below). The hippocampal patients were high functioning and did not have any cognitive impairments other than severe memory deficits (see Supplementary Materials Table S1; Mullally et al., 2012).

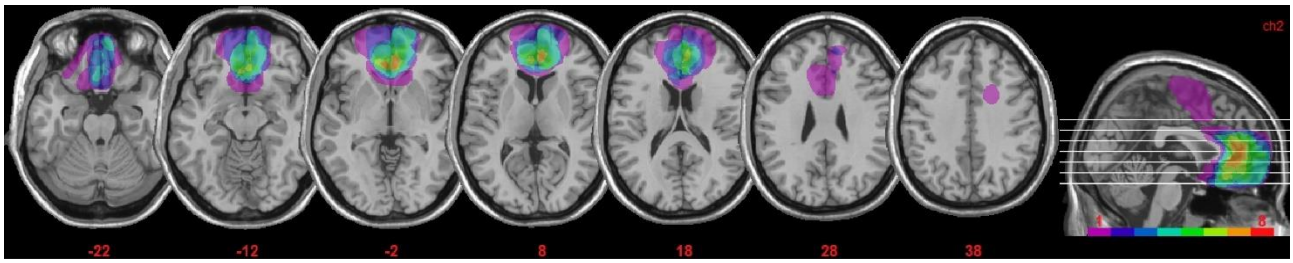
Lesion analysis

vmPFC and control patients' individual lesions, derived from magnetic resonance imaging or computerized tomography images, were manually drawn by an expert neurologist (not involved in the present study, and blind to task performance), or by F.D.L, and then verified by the same neurologist, directly on each slice of the normalized T1-weighted template MRI scan from the Montreal Neurological Institute (Holmes et al., 1998). This template is approximately oriented to match Talairach space (Talairach & Tournoux, 1988) and is distributed with MRIcro (Holmes et al., 1998). This manual procedure combines segmentation (identification of lesion boundaries) and registration (to a standard template) into a single step, with no additional transformation required (Kimberg, Coslett, & Schwartz, 2007). MRIcro software was used to estimate lesion volumes (in cc) and generate lesion overlap images.

Figure 6 shows the extent and overlap of brain lesions in vmPFC patients. The Brodmann areas (BA) that were mainly affected were BA 10, BA 11, BA 24, BA 25, BA 32, with the region of maximal overlap occurring in BA 11 (M = 17.30 cc, SD = 9.85), BA 10 (M = 8.79 cc, SD = 6.65), and BA 32 (M = 6.06 cc, SD = 3.34). One vmPFC patient had a very large lesion that extended to dorsal prefrontal cortex (BA 6 and BA 8). Excluding this patient from the analyses, however, did not alter the results. For the control patients, the areas mainly affected were BAs 17-19 (M = 5.68 cc, SD = 9.08), BAs 20-22 and BA 37 (M = 14.06 cc, SD = 20.81), and BAs 39-40 (M = 2.90 cc, SD = 5.58). There was no significant difference in lesion volume between vmPFC patients and control patients (42.61 vs. 40.38 cc, t = 0.12, p = 0.91). The hippocampal patients had selective

bilateral hippocampal damage as confirmed by manual segmentation of the hippocampi and automated whole-brain grey matter analyses as described in Mullally et al. (2012).

Figure 6. Representative axial slices and cumulative midsagittal view of the standard Montreal Neurological Institute brain showing the extent of lesion overlap in the vmPFC patients. The white horizontal lines on the sagittal view are the positions of the axial slices, and the red numbers below the axial views are the z coordinates of each slice. The color bar indicates the number of overlapping lesions. Maximal overlap occurs in BA 10, 11, and 32. The left hemisphere is on the left side.



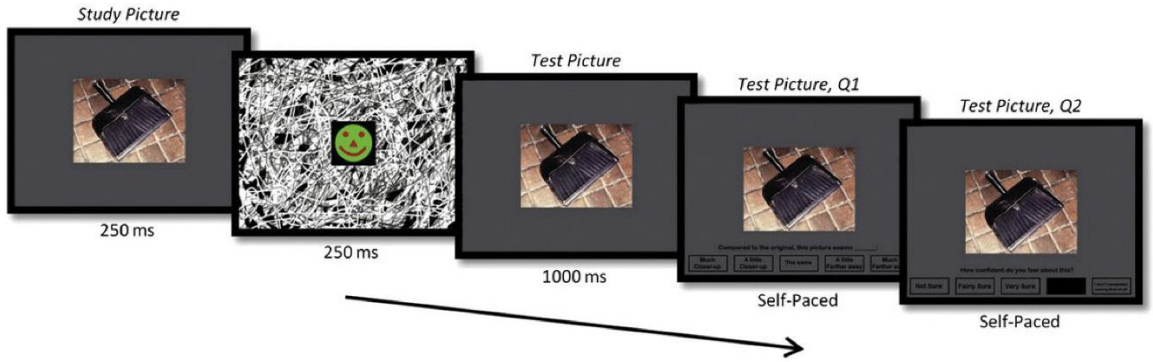
Tasks

Rapid Serial Visual Presentation Task

BE was measured with the same Rapid Serial Visual Presentation Task used by Mullally et al. (2012) (see Figure 7). Participants were informed that, on each trial, they would be viewing a picture of a simple scene twice in rapid succession, and upon the second presentation of the scene they would have to decide whether the scene was exactly the same as they had seen before, or if instead it was closer-up or farther-away. They were told that the purpose of the experiment was to determine how well people can focus their attention. After having seen an example stimulus (e.g., a pink flower on a green background, in standard and closer-up view), participants completed 24 randomly presented trials. In all cases, the initial picture comprised a single, centrally positioned object in a simple scene, presented on the computer screen for 250 ms and followed by a briefly presented (250 ms) visual noise mask. The second picture immediately followed the mask. The task was to rate the second picture relative to the first, choosing one of five options, i.e., “much closer-up”, “a little closer-up”, “the same”, “a little farther-away” or “much farther-away”. Unbeknownst to the participants, the two pictures were always identical, and thus all picture pairs should have been rated as the same (the correct answer).

The proportion of trials classified as either 'the same', 'closer-up' (collapsing across 'much closer-up' and 'a little closer-up' responses), or 'farther-away' responses (collapsing across 'much farther-away' and 'a little farther-away' responses) was calculated as the percentage of responses made in each category relative to the total number of responses made. BE is revealed by a disproportionally large number of incorrect "closer-up" responses. This is because when they initially view a scene, participants typically imagine the extended environment surrounding the scene. When this more expansive representation is subsequently compared with the second 'test' picture, although it is identical to the initial picture viewed only 250ms previous, it is consistently believed to depict a closer-up scene. In addition, BE can be quantified by a mean BE score, calculated by averaging the numerical values across the 24 trials associated with the responses, i.e., "much closer-up" = -2; "a little closer-up" = -1; "the same" = 0; "a little farther-away" = +1; "much farther-away" = +2. The BE score indicates the degree of bias towards one response over another, with a mean score of '0' indicating no BE effect, and negative scores reflecting BE. On each trial participants also reported how confident they were about their decision using a three-point scale (1 = "not sure", 2 = "fairly sure", 3 = "very sure"), and mean confidence ratings were calculated for each of the three response categories (the same, closer-up, farther-away). Given the rapid presentation of the first scene on each trial, they were also given the option to press a button to indicate that they did not see the first picture at all (5 = "don't remember"). The frequency with which this happened was very low (vmPFC patients: 4 trials; control patients: 5 trials; vmPFC healthy controls: 1 trial), as is typical in BE research, and this did not differ significantly across groups ($H = 2.68$; $p = 0.26$). These trials were discarded from subsequent analyses.

Figure 7. Rapid Serial Visual Presentation Task. Timeline of an example trial. First, a simple scene was presented for 250 ms, followed by a brief mask which was also presented for 250 ms. The scene image was then presented again for 1000 ms, after which a rating scale appeared underneath. The participants were asked to rate whether the two scenes were the same, or whether the second scene was a closer-up or farther-away view compared to the first scene. Participants then rated how confident they were in their decision.



Scene Probe Task

Using a 'scene probe' task we attempted to ascertain what aspects of a scene representation might be affected by vmPFC damage. As with the hippocampal-lesioned patients in Mullally et al. (2012), a close-up photograph of a scene was displayed and remained on the screen for the duration of the task (see Figure 8). Participants were first asked to name the main components of the scene, namely, the central object (a bench), the background (trees and houses), the type of place where the photograph was taken (a park/garden), and the predominant colors (green and brown). A score of 1 was awarded to each of the four elements of the scene correctly listed, and a score of 0 for missing elements (range 0-4). Participants were then asked to describe in as much detail as possible what the scene might be like beyond the boundaries of the current view, that is, what might come into view if they imagined taking a few steps back from the camera's current position. Participants were encouraged to use their imagination. Verbal descriptions were recorded and later transcribed. Every statement was classified as belonging to one of four categories: entities present (EP, e.g., "there is a bench"), sensory descriptions (SD, e.g., "the chair is made of wood"), spatial references (SPA; e.g., "behind the tree"), and thoughts/emotions/actions (TEA, e.g., "I felt lonely") (Mullally et al., 2012; see also Hassabis et al., 2007). Participants were also asked whether they were actually able to visualize the extended scene in their imagination and rate the vividness of the scene beyond the view using a 5-point scale (1 = not vivid at all…5 = very vivid). If they were unable to visualize anything, they were given a score of 0. All descriptions were scored by author FDL (not blind to group membership), and a second rater (blind to group membership) scored 1/3 of the transcripts

independently. Inter-rater reliability (separately for SD, SPA, EP, TEA), assessed with intra-class correlations (Mcgraw & Wong, 1996), was high (coefficients > 0.76 in all cases).

Figure 8. Scene probe task. The image depicts the scene stimulus used. Participants were instructed to describe this picture out loud, including the main object and background. They were then asked what would come into view if they stepped back from the current camera position.

Data analyses

Given that in most cases the dependent variables were non-normally distributed (Kolmogorov-Smirnov $d > 0.13$, $p < 0.05$), behavioral data were analyzed with non-parametric tests. We compared vmPFC patients with vmPFC healthy controls and control patients. We also compared the three patient groups (vmPFC, hippocampal and control patients) directly. We did this by calculating z-scores for each patient with reference to their respective matched healthy control group (e.g., vmPFC healthy controls for vmPFC patients and control patients, and hippocampal healthy controls for hippocampal patients), and comparing z-scores across patient groups. This allowed us to control for age and education differences between the Italian and British patient cohorts. We analyzed comparisons involving the three participant groups with non-parametric Kruskall-Wallis analyses of variance (ANOVA) and conducted planned comparisons between vmPFC patients and brain-damaged and healthy controls with Mann-Whitney z tests - we report the exact, two-tailed, uncorrected p values. Where appropriate, we also report effect sizes (r) for non-normal data (based on Fritz, Morris, & Richler, 2012) where a large effect is > 0.5, a medium effect

~ 0.3, and a small effect is ~ 0.1 (Coolican, 2009). All differences were considered statistically significant at $p < 0.05$, two-tailed.

Results

Rapid Serial Visual Presentation Task

Accuracy. Figure 9A shows the boxplots of the percentage of each response type (closer-up, the same, farther-away), collapsing across the degrees of subjective distance ("much" or "a little" farther/closer), by participant group. Figure 10A shows the boxplots of the boundary extension (BE) score by participant group. BE was apparent in all groups, as evidenced by no group selecting the correct - 'same'- response 100% of the time. However, whereas healthy controls and control patients rated more often the second presentation of pictures as closer-up, vmPFC patients (and hippocampal patients) rated more often the pictures correctly as being the same, and thus showed attenuated BE. Statistical tests confirmed these observations. Kruskal-Wallis ANOVAs on the percentage of the same, closer-up, and farther-away responses across participant groups (vmPFC patients, control patients, vmPFC healthy controls) showed significant group differences for the same ($H = 9.68$, $p = 0.01$) and closer-up responses ($H = 8.24$, $p = 0.02$). Post hoc Mann-Whitney tests showed that vmPFC patients classified trials more often as the same compared to both vmPFC healthy controls ($U = 9.00$, $Z = 2.75$, $p = 0.01$, $r = 0.65$), and control patients ($U = 10.00$, $Z = 2.66$, $p = 0.01$, $r = 0.63$), and less often as closer-up compared to both vmPFC healthy controls ($U = 11.50$, $Z = -2.53$, $p = 0.01$, $r = 0.60$) and control patients ($U = 12.50$, $Z = -2.44$, $p = 0.01$, $r = 0.58$). There were no differences in the percentage of trials classified as the same ($p = 0.91$, $r = 0.03$) or closer-up ($p = 0.70$, $r = 0.1$) between vmPFC healthy controls and control patients. Similarly, there were significant group differences in the BE score ($H = 6.11$, $p = 0.047$), such that vmPFC patients showed a lower BE score than vmPFC healthy controls ($U = 15.50$, $Z = 2.18$, $p = 0.03$, $r = 0.51$) and control patients ($U = 16.00$, $Z = 2.13$, $p = 0.03$, $r = 0.50$), while there were no differences between the two control groups ($p = 0.97$, $r = 0.01$). This first set of analyses shows that vmPFC patients

have a significantly reduced BE compared to both healthy and brain-damaged controls. vmPFC performance was reminiscent of that of hippocampal patients, who also showed attenuated BE (Mullally et al., 2012).

To compare BE across vmPFC patients, hippocampal patients and control patients directly, we analyzed z-scores (see Figure 9B and Figure 10B). Kruskal-Wallis ANOVAs on z-scores showed significant group differences in the percentage of the same ($H = 8.14$, $p = 0.02$), closer-up ($H = 7.32$, $p = 0.03$) and, a strong trend in the BE score ($H = 5.66$, $p = 0.059$). There were no differences in the percentage of farther-away responses ($H = 2.06$, $p = 0.36$). Mann-Whitney post hoc tests showed that, compared to control patients, both vmPFC and hippocampal patients more often gave the correct (the same) response (vmPFC vs. control patients: $U = 10.00$, $Z = 2.62$, $p = 0.01$, $r = 0.62$; hippocampal vs. control patients: $U = 14.00$, $Z = 2.00$, $p = 0.04$, $r = 0.49$) and less often the closer-up responses (vmPFC vs. control patients: $U = 12.50$, $Z = -2.40$, $p = 0.02$, $r = 0.57$; hippocampal vs. control patients: $U = 14.00$, $Z = -2.00$, $p = 0.04$, $r = 0.49$). Importantly, there was no difference in the percentage of same, closer-up and farther-away responses between vmPFC and hippocampal patients (all $p > 0.69$, all $r < 0.1$), indicating that BE was reduced to a similar degree. Confirming these results, BE scores were similar between vmPFC and hippocampal patients ($p = 0.60$, $r = 0.13$), and were lower in vmPFC patients ($U = 16.00$, $Z = 2.09$, $p = 0.04$, $r = 0.49$), and hippocampal patients ($U = 17.00$, $Z = 1.71$, $p = 0.09$, $r = 0.41$) compared to control patients, although only the difference between vmPFC and control patients reached statistical significance. Together, the z-score results confirmed that vmPFC patients, as well as hippocampal patients, showed a reduced BE effect compared to patients with brain lesions not involving vmPFC or the hippocampus.

Figure 9. A: Box-plots of the percentage of trials classified as the same, closer-up and farther-away in the Rapid Serial Visual Presentation Task by participant group. The data and significance levels contrasting patients with hippocampal damage and their controls are from Mullally et al. (2012). B: Box-plots of z-scores for the same, closer-up, and farther-away responses for the three patient groups. Boxplots depict the median, first and third quartiles, and minimum and maximum (whiskers) of the data sets. *$p < 0.05$.

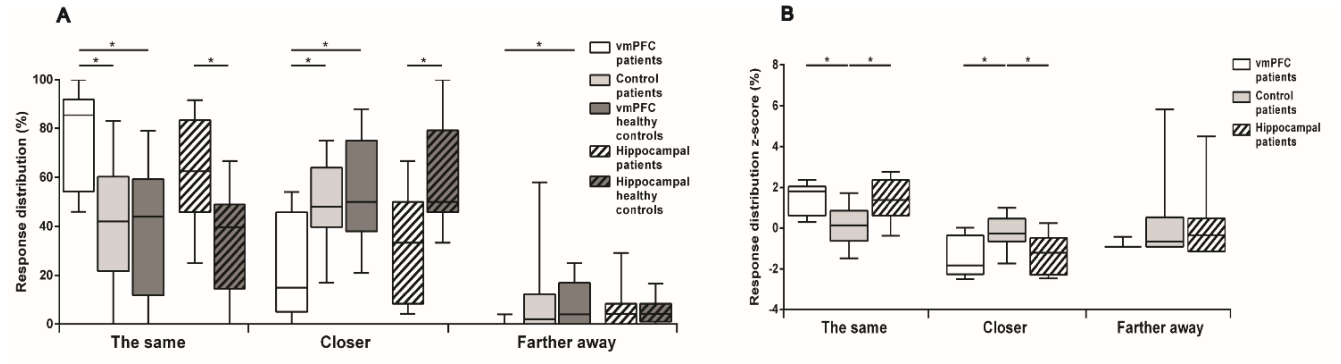
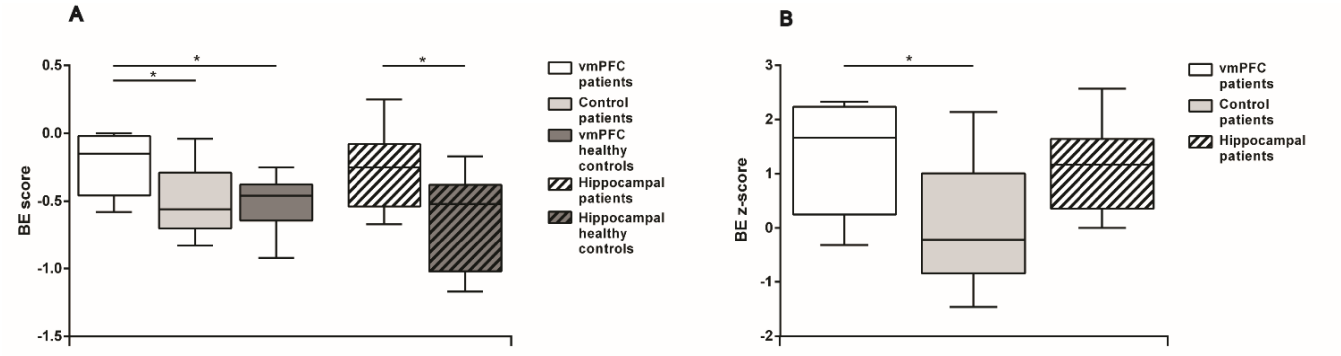


Figure 10. A: Box-plots of boundary extension (BE) scores by participant group. The data and significance levels contrasting patients with hippocampal damage and their controls are from Mullally et al. (2012). The more negative the score, the more BE. B: Box-plots of BE z-scores for the three patient groups. Boxplots depict the median, first and third quartiles, and minimum and maximum (whiskers) of the data sets. *p < 0.05.



Confidence. Table 12 shows confidence ratings by participant group and type of response. Kruskal-Wallis ANOVAs on confidence ratings associated with the same, closer-up, and farther-away responses across participant groups (vmPFC patients, control patients, vmPFC healthy controls) showed significant group differences in confidence ratings for closer-up responses ($H = 6.84$, $p = 0.03$), but not for the other response categories ($p > 0.18$ in both cases). Post hoc tests showed that vmPFC patients were less confident in their closer-up responses than vmPFC healthy controls ($U = 12.00$, $Z = -2.24$, $p = 0.02$, $r = 0.54$), but had similar confidence levels as the control patients ($p = 0.22$, $r = 0.30$). There was no significant difference in confidence for closer-up responses between control patients and vmPFC healthy controls ($p = 0.07$, $r = 0.41$). Comparing vmPFC patients, hippocampal patients, and control patients directly using z-scores showed there were no significant group differences in confidence associated with the same, closer-up, or farther-away responses ($p > 0.07$ in all cases).

Table 12. Confidence ratings in the Rapid Serial Visual Presentation Task by participant group.

	The same	Closer-up	Farther-away	Same z-score	Closer-up z-score	Farther-away z-score
vmPFC patients	2.60 (1.90-2.96)	2.00 (1.77-3.00)	2.00[1]	0.37 (-1.26-1.16)	-1.24 (-1.98-2.00)	0.33
Control patients	2.10 (1.71-2.43)	2.07 (1.86-2.60)	1.83 (1.00-2.00)	-0.80 (-1.69- -0.05)	-1.00 (-1.70-0.71)	-0.09 (-2.16-0.33)
vmPFC healthy controls	2.21 (2.00-3.00)	2.29 (2.00-3.00)	2.00 (1.00-2.25)	-	-	-
Hippocampal patients	2.17 (1.36-2.88)	1.78 (1.00-2.42)	2.00 (1.00-2.00)	0.53 (-1.68-2.47)	-1.14 (-2.84-0.25)	0.88 (-3.15-0.88)
Hippocampal healthy controls	1.97 (1.33-2.62)	2.17 (1.75-3.00)	1.75 (1.00-2.00)	-	-	-

Notes. Median and range (in parentheses) of confidence scores. vmPFC = ventromedial prefrontal cortex. Z-scores refer to the difference between patients' scores and the average score of their healthy control group, divided by the standard deviation of the healthy control group. [1] = only one patient gave a farther-away response, therefore no range is reported. Confidence was rated on a three-point scale: 1 = "not sure", 2 = "fairly sure", 3 = "very sure".

As a side note, given that some of the control patients had visual field deficits, one may ask whether these deficits played a role in their (normal) performance on the BE task. For example, did these patients fail to appreciate that the pictures were the same across presentations because they did not scan them completely? We therefore inspected BE scores separately for control patients with and without visual field deficits. Control patients with (M = -0.47) and without visual deficits (M = -0.56) had comparable BE scores (Mann-Whitney U = 7.50, Z = 0.68, p = 0.49, r = 0.22), and these were similar to those of the healthy controls (M = -0.51; healthy controls vs. control patients with visual field deficits: U = 34.00, Z = -0.10, p = 0.92, r = 0.02; healthy controls vs. control patients without visual field deficits: U = 13.50, Z = 0.25, p = 0.80, r = 0.1).

Scene Probe Task

Contents. Upon presentation of the scene probe, all participants were able to list the main elements of the scene, with the exception of one vmPFC patient who failed to mention the location, two control patients who failed to mention, in one case the location, and in the other case the colors, and two healthy controls who failed to mention the colors. The description scores were consequently very high, and comparable across participant groups (vmPFC patients: 3.88; control

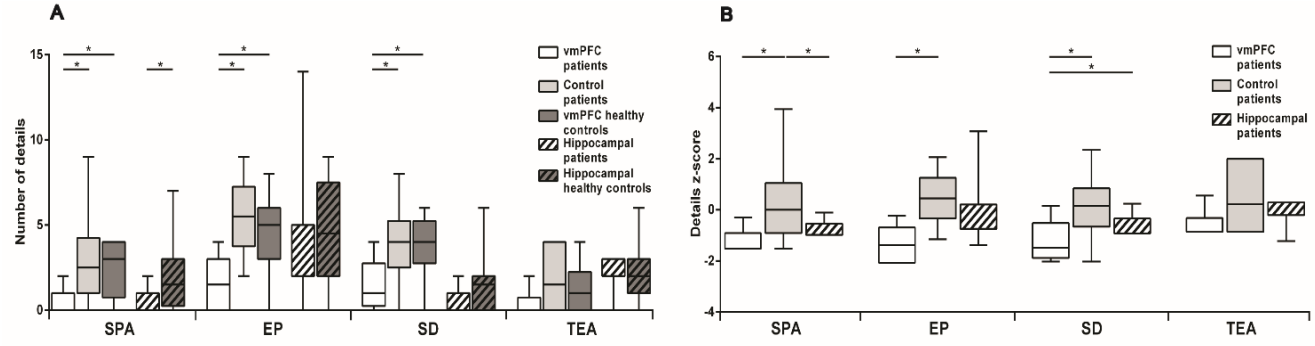
patients: 3.80; healthy controls: 3.80; H = 0.21, p = 0.90). All hippocampal patients and their controls named all of the elements (score = 4 in all cases).

Figure 11A shows the boxplots of the number of details participants produced when requested to imagine what might be beyond the boundaries of the current view, by participant group and content category. Kruskal-Wallis ANOVAs across participant groups (vmPFC patients, control patients, vmPFC healthy controls) showed significant group differences in the number of entities present (EP; H = 10.73, p = 0.01), sensory descriptions (SD; H = 6.97, p = 0.03), and spatial references (SPA; H = 8.46, p = 0.01), but not thoughts/actions/emotions (TEA; p = 0.17). Mann-Whitney post-hoc tests showed that vmPFC patients produced fewer EP, SD, and SPA than both vmPFC healthy controls (EP: U = 11.00, Z = -2.58, p = 0.01, r = 0.61; SD: U = 14.00, Z = -2.31, p = 0.02, r = 0.54; SPA: U = 13.50, Z = -2.35, p = 0.02, r = 0.55) and control patients (EP: U = 6.50, Z = -2.98, p = 0.003, r = 0.70; SD: U = 15.00, Z = -2.22, p = 0.03, r = 0.52; SPA: U = 10.50, Z = -2.62, p = 0.01, r = 0.62), whereas no differences emerged between vmPFC healthy controls and control patients across content categories ($p > 0.45$, $r < 0.2$ in all cases). Thus, consistent with evidence of reduced BE, vmPFC patients had difficulty imagining what might be beyond the scene they were currently perceiving. Their construction of the extended scene, however, differed from that of hippocampal patients, which was specifically devoid of spatial references compared to that of the hippocampal healthy controls, while EP, SD and TEA categories were intact (see Mullally et al. 2012).

The analysis of z-scores (Figure 11B) confirms that deficits in imagining what would be beyond the view differed between vmPFC and hippocampal patients. Kruskal-Wallis ANOVAs across participant groups (vmPFC patients, hippocampal patients, control patients) revealed significant group differences in the number of EP (H = 9.81, p = 0.01), SD (H = 7.50, p = 0.02), and SPA (H = 9.39, p = 0.01), but not TEA (p = 0.17). Both vmPFC patients (U = 10.50, Z = -2.58, p = 0.01, r = 0.61) and hippocampal patients (U = 13.00, Z = -2.10, p = 0.04, r = 0.51) produced fewer SPA than controls patients. However, vmPFC patients' reports were also impoverished with regard

to EP (U = 6.50, Z = -2.93, p = 0.003, r = 0.69) and SD (U = 15.00, Z = -2.18, p = 0.03, r = 0.51) than those of controls patients, whereas hippocampal patients' reports were not (p > 0.13, r < 0.4 in both cases). In addition, vmPFC patients produced significantly fewer SD than hippocampal patients (U = 8.00, Z = -2.26, p = 0.02, r = 0.58), while SPA and EP were not significantly different between vmPFC and hippocampal patients (p > 0.12, r < 0.4 in both cases).

Figure 11. A: Box-plots of the number of constructed details in the scene probe task, with SPA = spatial references; EP = entities present, SD = sensory descriptions; TEA = thoughts/emotions/actions. The data and significance levels contrasting patients with hippocampal damage and their controls are from Mullally et al. (2012). B: Box-plots of z-scores for details produced in the scene probe task for the three patient groups. Bars represent standard errors of the mean. Boxplots depict the median, first and third quartiles, and minimum and maximum (whiskers) of the data sets. *p < 0.05.



Vividness. Table 13 reports self-rated vividness for the imagined extended scene by patient group. A Kruskal-Wallis ANOVA on vividness ratings revealed significant differences among vmPFC patients, control patients, and vmPFC healthy controls (H = 8.73, p = 0.01), such that vmPFC patients (U = 10.00, Z = -2.67, p = 0.01, r = 0.63) and control patients (U = 24.00, Z = 1.97, p = 0.049, r = 0.44) judged the extended scene as less vivid than did healthy controls, with no difference between vmPFC patients and control patients (p = 0.28, r = 0.25). Hippocampal patients, too, rated the extended scenes they had imagined as less vivid than their healthy controls (Mullally et al., 2012). When we compared the three patient groups directly using vividness z-scores, we found no group differences (p = 0.43).

Table 13. Vividness ratings and z scores in the scene probe task by participant group.

	vmPFC patients	Control patients	vmPFC healthy controls	Hippocampal patients	Hippocampal healthy controls
Vividness	1.50 (0.00-4.00)	3.00 (0.00-5.00)	4.00 (3.00-5.00)	0.00 (0.00-5.00)	5.00 (1.66-5.00)
Vividness z-score	-4.58 (-7.22- -0.18)	-1.94 (-7.22-1.59)	-	-3.04 (-3.04-0.74)	-

Notes. Median and range (in parentheses) of vividness scores. vmPFC = ventromedial prefrontal cortex. Vividness was rated using a five-point scale: 1 = not vivid at all…5 = very vivid.

Discussion

This study investigated whether vmPFC is involved in rapid, automatic and implicit visual scene construction. To examine this, we exploited BE, a cognitive phenomenon whereby, upon viewing a scene, individuals automatically construct an internal representation of the scene that extends beyond its given borders, which is revealed by the subsequent misremembering of the extended scene instead of the original (Intraub, 2012). We contrasted performance of patients with vmPFC damage to that of control patients with (mainly) occipital lesions, healthy controls, and the hippocampal patients described in Mullally et al. (2012). The results showed that vmPFC patients have significantly reduced BE compared to healthy individuals, and the attenuation of BE was comparable to that previously observed in hippocampal-damaged patients (Mullally et al., 2012). These findings extend previous evidence of impaired scene construction in hippocampal patients by showing that vmPFC, alongside the hippocampus, is necessary to automatically construct internal representations of (extended) scenes. Importantly, we show that it is not the case that brain damage per se disrupts BE. Control patients with lesions located mainly in the occipital cortex (including those with and without visual field defects) showed BE that was similar to that of healthy controls.

The reduced BE in vmPFC (as well as hippocampal) patients cannot be attributed to a failure of memory between study and test, because it indicates that patients were in fact less prone to the error of commission made by the healthy controls, and so paradoxically outperformed healthy controls in remembering the scenes accurately. Instead, our results suggest that vmPFC (and

hippocampal) patients may have a fundamental difficulty with the mental construction of scene representations. Before discussing this further, it is important to consider whether the adoption of a response heuristic or a tendency towards perseveration on the part of the vmPFC patients may have had an impact on our findings. We think it unlikely, because only one vmPFC patient always selected the 'same' response option across all trials, and the results do not change if we exclude his data from the analyses. Moreover, any tendency towards perseveration should be manifest across response types. However, the two vmPFC patients who started with a 'closer up' response did not perseverate in responding closer up on the subsequent trials, and instead switched soon to 'same' responses, as did the other vmPFC patients following their occasional 'closer up' responses. Moreover, vmPFC patients' rare errors were not random, but were in the same direction as the controls' - they mostly consisted of closer up responses, whereas farther away responses were rare in all groups.

We propose that reduced BE in the vmPFC patients indicates a problem in the mental construction of scenes, consistent with the fact that vmPFC is part of a distributed network of brain regions engaged during scene construction (Hassabis et al., 2007; Hassabis & Maguire, 2007). That vmPFC patients have reduced BE accords with previous evidence that vmPFC patients are impaired at constructing personal past and future events, and also future events that involve other people or atemporal fictitious events (Bertossi et al, 2016a,b). This is because the ability to mentally construct spatially coherent scenes is likely necessary to mentally represent and experience any complex event as an alternative to direct (perceptual) experience. In this regard, it is also notable that patients with vmPFC damage initiate fewer mind-wandering episodes compared to patients with other brain lesions or healthy controls (Bertossi & Ciaramelli, 2016; see also McCormick, Rosenthal, Miller, & Maguire, 2018). Gathering additional convergent evidence for impaired scene construction in vmPFC patients from a BE paradigm, however, is particularly important. First, as we have demonstrated with the study 2 in the previous chapter, unlike hippocampal patients (Race et al., 2011; Race, Keane, & Verfaellie, 2013; Race, Keane, & Verfaellie, 2015), vmPFC patients may

have impaired narrative skills (Bertossi et al., 2017). This can contribute to their poor descriptions of past and future events (Bertossi et al., 2017), but certainly not to their reduced BE, because BE does not depend on language. Second, whereas previous research has investigated the voluntary and explicit construction of past and novel events in vmPFC patients (Bertossi et al, 2016a,b; Kurczek et al., 2015), BE is an automatic phenomenon, and therefore hardly attributable to lack of motivation or cognitive resources in vmPFC patients.

An important question is whether the role played by vmPFC and hippocampus can be differentiated. The results from the scene probe task suggest that they can be. Both patient groups proved able to describe the relevant components of the scene in view, but failed when they were asked to imagine taking a step back from the current position and describe what might then come into view. However, the reports of vmPFC- and hippocampal-damaged patients were qualitatively different. Hippocampal patients' reports contained abnormally fewer spatial references but were not different from their controls in terms of other types of details. In contrast, vmPFC patients' reports were poor not only in terms of spatial references but also in the other types of details, including entities present and their sensory details. Thus, scenes lacked primarily spatial coherence in hippocampal patients, whereas they additionally lacked content in vmPFC patients, replicating previous findings of impoverished simulated future and fictitious experiences (Bertossi et al, 2016a), and suggesting a more general role for vmPFC in scene construction. Of course, unlike the BE task, the scene probe task depends on language, and therefore one concern might be that a deficit in narrative ability or generally reduced verbal output may have contributed to a reduction in performance, especially in the case of vmPFC patients who produced fewer details of all types. We consider this possibility unlikely, however. First, vmPFC patients had normal verbal fluency, and no problem describing the scene that was in view. Note also that the number of different types of imagined details in the scene probe task (EP, SD, SPA, TEA) did not correlate with each other ($p > 0.35$ in all cases) nor with phonemic or semantic fluency ($p > 0.27$ in both cases). Moreover, in our

previously reported study 2, we showed that impaired narrative skills do not explain poor episodic future thinking in vmPFC patients (Bertossi et al., 2017).

We propose that vmPFC and the hippocampus work in concert during scene construction, by playing different but complementary roles (McCormick, Ciaramelli, De Luca, & Maguire, 2018). vmPFC initiates the scene construction process by predicting and then coordinating the activation of relevant schematic knowledge (e.g., the prototypical park) (Burgess & Shallice, 1996; Ghosh, Moscovitch, Melo Colella, & Gilboa, 2014; Van Kesteren, Ruiter, Fernandez, & Henson, 2012) which the hippocampus uses to build a first, rudimentary spatially coherent representation which includes the extended scene. The vmPFC then engages in iterations via feedback loops with neocortex and hippocampus, mediating the prediction, retrieval, monitoring, and integration of relevant elements from neocortical areas (e.g., what is typically in a park) (Moscovitch, 1992; Benoit, Szpunar, & Schacter, 2014; Moscovitch et al., 2016; McCormick, Ciaramelli, et al., 2018) to enrich the initial spatial sketch with appropriate details, resulting in a complex and content-rich scene. This hypothesis is in line with the finding that hippocampal patients can produce appropriate scene contents, but these appear to be "floating" in an ill-defined space, whereas vmPFC patients produce scenes poor in both spatial context and content. Of course, even though our results indicate that vmPFC is necessary to build even single scenes, its contribution is expected to be magnified during construction of complex unfolding events (McCormick, Ciaramelli, et al., 2018). This is because events additionally entail transitions between (and hence the construction of) multiple scenes, and the predictions about, and knowledge of, how common events typically unfold (e.g., a typical day in the park), which is also supported by medial prefrontal cortex regions (Krueger, Barbey, & Grafman, 2009). This may explain why vmPFC patients are particularly poor at processing extended mental events (Bertossi et al., 2016b).

To conclude, we have found that vmPFC patients show reduced BE, indicating that vmPFC is necessary for both explicit and implicit scene construction processes, along with the hippocampus. Scenes are the backbone of complex events such that events based on familiar

(compared to unfamiliar) scenes are experienced more vividly (de Vito, Gamboz, & Brandimonte, 2012; Robin & Moscovitch, 2014). Moreover, individuals who are asked to recall an event have been shown to initially set a spatial scene for the subsequent event to reside within (Robin, Wynn, & Moscovitch, 2015). Future studies will be needed to establish the precise contribution of the vmPFC, and whether it is necessary for all - prediction, retrieval, coordination, monitoring, integration of elements from neocortical areas - or just some of the processes involved in scene and event construction.

In particular, if, as we proposed, vmPFC is necessary to initiate the scene construction process and to integrate relevant elements to create a content-rich representation of a scene, vmPFC patients would be impaired in any task requiring to self-initiate the construction of scenes, be they single, as in the present study, or multiple, as in the previous studies requiring to simulate extended mental events (Bertossi et al., 2016a,b; Bertossi et al., 2017). Therefore, we speculate that if this self-initiation process is supported or supplied by tasks providing structured cues, the scene construction impairment shown by vmPFC patients could be circumvented. We test this hypothesis in the next study 4, using a scene processing task, which minimizes the self-initiation component of scene construction. We will again compare the performance of vmPFC patients to that of hippocampal patients, to further understand the different contribution that these two regions provide to the construction of scenes.

Supplementary Table S1. Summary of hippocampal-damaged patients' details.

ID	Sex	Age (yrs)	H'ness	Education	Aetiology	Chronicity (yrs)	Full Scale IQ	M.R. [a]	R.A. (yrs)	C.F. [b]	Recognition	Recall
A	M	63	R	University	LE	6	99	11	10	10	Unimpaired	Impaired
B	M	40	R	A-Levels	Anoxia	21	112	16	<1	2	Unimpaired	Impaired
C	M	37	R	University	LE	3.5	107	11	~25	1	Impaired	Impaired
D	F	32	R	University	LE	7	109	13	10	4	Borderline	Impaired
E	M	38	R	GCSE	LE	3.5	99	8	1	1	Impaired	Impaired
F	F	40	R	University	Unknown	22	105	14	18	5	Unimpaired	Impaired
G	F	40	L	University	Unknown	24	105	13	16	5	Unimpaired	Impaired

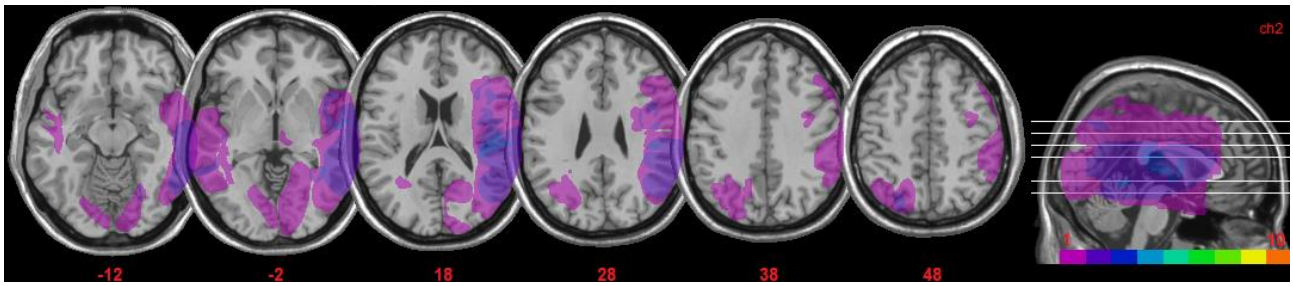
H'ness = handedness; A-Levels = school examinations taken at the point of leaving secondary school ~18 years of age; GCSE = school examinations taken ~14-16 years of age; LE = limbic encephalitis; Chronicity = number of years since the illness/incident precipitating the hippocampal damage/memory loss; [a] = Scaled score, Matrix Reasoning subtest of the WAIS-III; [b] = Complex Figure (Rey-Osterrieth /BMIBP) delayed recall (percentile score); R.A. = Retrograde Amnesia. See Mullally et al. (2012) for more details.

Supplementary Table S2. Mean percentage of accurate responses in visual detection and visual search tasks (Bolognini, Rasi, Coccia, & Làdavas, 2005; Passamonti, Bertini, & Làdavas, 2009) attained by control patients with hemianopia (N = 7).

Test	Visual detection: eye movements not allowed		Visual detection: eye movements allowed		Visual search: letters	Visual search: numbers
	R	L	R	L		
Control patients with left hemisphere lesions	34*	92	86	97	100	100
Control patients with right hemisphere lesions	98	58*	98	92	89	100

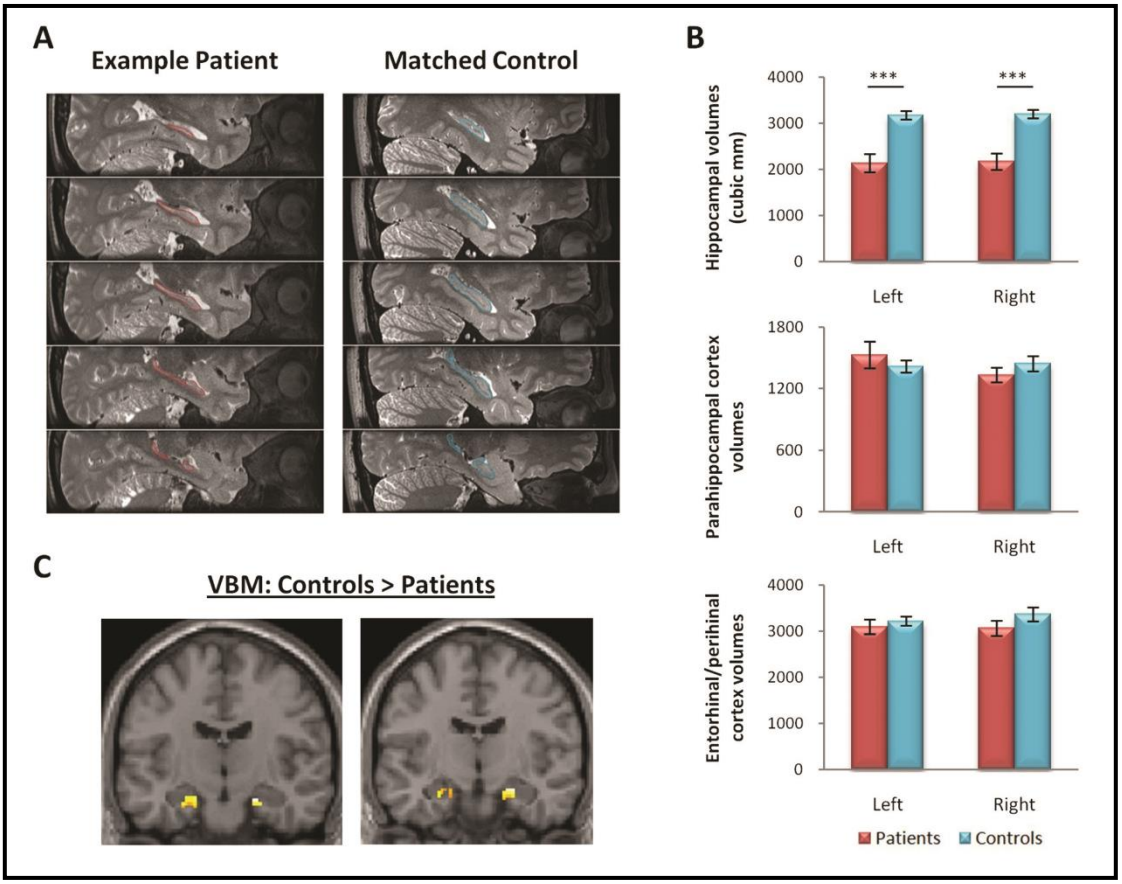
R = right hemifield, L = left hemifield. Asterisks highlight a pathological performance.

Supplementary Figure S1.



Extent and overlap of brain lesions for the control patients. The figure represents the patients' lesions projected on the same six axial slices of the standard Montreal Neurological Institute brain. The white horizontal lines on the sagittal view are the positions of the axial slices, and the red numbers below the axial views are the z coordinates of each slice. The color bar indicates the number of overlapping lesions. Maximal overlap occurred in BA 21-22, 37, 19. The left hemisphere is on the left side.

Supplementary Figure S2.



Lesion characterisation in the hippocampal-damaged patients. (A) An example high-resolution T2-weighted scan from a hippocampal patient and one of their matched controls. The outer boundary of the hippocampus is illustrated in red for the patient and blue for the control. (B) Volumetric measurements were extracted from the manually segmented medial temporal lobe regions. Significant reductions in hippocampal volume were observed in the patient group relative to the matched control group (***$p < 0.001$). By contrast, no significant volume differences were found in the parahippocampal or entorhinal/perirhinal cortices. (C) An automated VBM analysis was performed to identify regions, at a whole-brain level, where grey matter volume differed significantly between the control and patient groups. Selective reductions in grey matter volume were observed in the patients, relative to the control group, only in the left and right hippocampus (images are displayed at $P < 0.05$ uncorrected).

Supplementary Material - Example Descriptions.

Example responses on the scene probe task ("If you were taking the picture and you took a few steps backwards, what do you think would come into view?").

vmPFC patient n.6: “If it [the picture] expands enough, there will be some people, children playing, there are some branches, quite big, I am not sure if it is possible to see whether it has any fruit, but I do not think it does.”

Control patient n.7: “I imagine that if I get farther, there could be a small artificial lake in front of the bench, where there might be small colored carps, or some water lilies or some water hyacinths, anybody can sit on the bench to relax, watching the water. On one side there could be a fountain, which would delimit this lake, and on the other side there could be a small flatter and a free area where kids play and parents, seated on the bench, watch them. Farther away, you can see better the roof of the house, the visible part seems like a skylight, I imagine the high part as quite pointy, tilted, similar to a Nordic environment, and the attic windows and another chimney on the left are also visible.”

Healthy control n.7: “I could see a trash can on one side, a lamppost, it's a lamppost working also as a trash can. I could also see a Coke can on the ground. Maybe the border of a pavement, cobbled with bricks, like cement covered with stones. If I went farther, I would see a bigger portion of the house, maybe one more window. On this side there could be a window, and on the other side there could be more plants.”

Study 4. Constructive and semantic scene processing following damage to the ventromedial prefrontal cortex or hippocampus.

Co-authored with Cornelia McCormick, Clive R. Rosenthal, Thomas D. Miller, Elisa Ciaramelli, and Eleanor A. Maguire.

(De Luca F, McCormick C, Rosenthal CR, Miller TD, Ciaramelli E, Maguire EA. Under revision, *Hippocampus*)

Introduction

The ventromedial prefrontal cortex (vmPFC) and the hippocampus are interconnected brain regions that form part of a wider network that supports key cognitive functions including autobiographical memory, future-thinking and spatial navigation (Svoboda, McKinnon, & Levine, 2006; Addis, Wong, & Schacter, 2007; Hassabis & Maguire, 2009; Spreng, Mar, & Kim, 2009). Patients with either bilateral vmPFC or hippocampal damage exhibit significant impairments across all of these domains (Maguire, Nannery, & Spiers, 2006; Ciaramelli, 2008; McCormick, Ciaramelli, De Luca, & Maguire, 2018). Given that the vmPFC and hippocampus seem to be critical for many of the same cognitive functions, this begs the question as to the nature of their specific contributions. This is important to establish if we are to gain a full understanding of how functions such as memory and future-thinking are instantiated in the brain. McCormick, Ciaramelli, et al. (2018) recently reviewed the neuropsychological literature with a specific focus on the effects of either bilateral vmPFC or hippocampal lesions. While they documented the impairment parallels, they also noted that the reasons for the deficits appeared to be different for the two types of patients.

Hippocampal-damaged patients ('hippocampal patients') have problems recalling the past and imagining the future, but they also cannot imagine even a single static scene. A scene is defined as a naturalistic three-dimensional spatially coherent representation of the world typically populated by objects and viewed from an egocentric perspective (Maguire & Mullally, 2013; Dalton, Zeidman, McCormick, & Maguire, 2018). This inability to construct scene imagery has been proposed to be a primary function of the hippocampus, and a vital ingredient for the proper operation of autobiographical memory, future-thinking and spatial navigation (Hassabis & Maguire,

2007; Maguire & Mullally, 2013; Zeidman & Maguire, 2016). Given that scene imagery is deployed widely across cognition, hippocampal patients should show deficits wherever scene imagery is required or is advantageous. Indeed, this is what has been found, with altered decision-making (McCormick, Rosenthal, Miller, & Maguire, 2016), mind-wandering (McCormick, Rosenthal, Miller, & Maguire, 2018) and scene perception (Lee et al., 2005; Mullally, Intraub, & Maguire, 2012) compared to healthy controls. Of note, while able to describe pictures of scenes accurately (Race, Keane, & Verfaellie, 2011; Race, Keane, & Verfaellie, 2013), when asked to imagine what might be beyond the view in a scene, hippocampal patients could generate appropriate details, but their descriptions lacked spatial references and they could not visualise what was beyond the borders of the scene image (Mullally et al., 2012).

On the face of it, patients with vmPFC damage ('vmPFC patients') seem to have highly similar problems as hippocampal patients, even down to apparently poor scores on a scene construction test (Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016). However, some points of divergence are notable. For example, unlike hippocampal patients, those with vmPFC lesions may show confabulation – the unintentional production of false memories (Whitlock, 1981; Moscovitch, 1995; Moscovitch & Melo, 1997; Johnson, O'Connor, & Cantor, 1997; Ciaramelli, Ghetti, Frattarelli, & Làdavas, 2006). vmPFC patients also fail to generate as many autobiographical event memories as healthy controls during free recall tasks (Della Sala, Laiacona, Spinnler, & Trivelli, 1993; Kopelman, Stanhope, & Kingsley, 1999; Bertossi, Tesini, Cappelli, & Ciaramelli, 2016). However, again, in contrast to hippocampal patients, vmPFC patients could accurately recall and describe specific individual scenes from autobiographical events if cued (Jake Kurczek et al., 2015). This suggests that they may retain a basic capacity for generating scene imagery when sufficiently cued (given their intact hippocampi). By contrast, we have shown in previous study 3 that when they were provided with a scene photograph and had to imagine what might be beyond the view, they were impaired at generating appropriate details of any kind (De Luca et al., 2018). In considering this and other evidence from across cognition, McCormick, Ciaramelli, et al. (2018)

concluded that while vmPFC lesions seem to leave patients able to react to external stimuli, they are impaired at initiating the endogenous processing needed for selecting and curating the appropriate content required for memory recall and scene construction.

A recently-developed task could provide further insights into the roles played by the vmPFC and hippocampus. McCormick et al.'s (2017) paradigm involves detecting either semantic (e.g., an elephant with butterflies for ears) or constructive (e.g., an endless staircase) violations in realistic scene images. Therefore, scene images can be semantically or constructively 'possible' or 'impossible'. Of note, the perceptual and general requirements of the tasks are comparable for the two types of scene. Patients with bilateral hippocampal damage were unimpaired when compared with control participants at judging whether scenes were semantically possible or impossible. However, they were significantly impaired at deciding if scenes were constructively possible or impossible. Control participants indicated during a post-task debriefing that they constructed flexible mental representations of the scenes in order to make constructive judgements. In contrast, the focus of the hippocampal patients was typically on specific fragments of the scenes, and there was little to suggest they constructed internal scene models. This finding adds further credence to the idea that the specific aspect of scene processing that is hippocampal-dependent appears to be the internal construction of scene imagery.

In the current study, we used the same possible/impossible scenes task to determine how patients with bilateral vmPFC damage would perform. If McCormick, Ciaramelli, et al.'s (2018) suggestion is correct, then with all of the information in front of them, and with an intact ability to construct scene imagery when heavily cued (i.e. by the scene stimuli), vmPFC patients should be able to detect impossibilities, be they constructive or semantic. This would be in clear contrast to the specifically constructive deficit displayed by hippocampal patients.

Methods

Participants

Twenty-four patients took part in the experiment. Eight patients had vmPFC damage (six males, mean age = 59.25 years, range = 46-74; see Table 14 for demographic and clinical information), and ten 'control patients' had brain damage that did not involve vmPFC or the hippocampus (eight males, mean age = 59.10 years, range = 45–77 years; Table 14). We also considered data from six patients who had hippocampal damage (all males, mean age = 57.00 years, range = 27–70 years). vmPFC and control patients were Italian and were recruited at the Centre for Studies and Research in Cognitive Neuroscience, Cesena, Italy. Hippocampal patients were British and were tested at the Wellcome Centre for Human Neuroimaging, University College London, UK. The background details of the hippocampal patients and their scores on the possible/impossible scenes task have already been reported in McCormick et al. (2017) (for convenience, background details are summarized in Table 15).

Brain damage in vmPFC patients was bilateral in all cases and resulted from the rupture of an anterior communicating artery (ACoA) aneurysm. In control patients, brain damage (left hemisphere: five cases; right hemisphere: five cases) was due to stroke (six cases), arteriovenous malformations (one case), intraparenchymal bleeding (one case), cerebral abscess (one case) or meningioma (one case). Lesion sites in control patients included the occipital cortex, occipital-temporal and occipital-parietal area, and lateral aspects of prefrontal cortex (see Supplementary Information Figure S3, and more on this below). The hippocampal-damaged patients' lesions were focal and bilateral (see Table 15 and McCormick et al., 2017). All patients were in a stable phase of health (see Tables 14 and 15 for information about chronicity), and had no other diagnoses likely to affect cognition or interfere with participation in the study (e.g., significant psychiatric disease, alcohol abuse, history of cerebrovascular disease).

Ten Italian healthy individuals (vmPFC healthy controls; all males; mean age = 57.90 years, range = 44-62; see Table 14) were matched to the vmPFC and control patients on age ($F_{(2,25)} = 0.07$, $p = 0.94$), education ($F_{(2,25)} = 0.00$, $p = 1.00$), and gender balance (vmPFC: $\chi^2 = 2.81$, $p = 0.09$; control patients: $\chi^2 = 2.22$, $p = 0.14$). The hippocampal patients were matched with twelve British

healthy individuals (hippocampal healthy controls; all males, mean age = 57.17 years, range = 31–77; see Table 15 and McCormick et al., 2017) on age (t = -0.02, p = 0.98), IQ (t = -0.75, p = 0.46) and gender balance (χ^2 = 0.00, p = 1.00). Healthy control participants were not taking psychoactive drugs and were free of current or past psychiatric or neurological illness as determined by history.

Participants gave informed consent in accordance with the Bioethical Committee of the University of Bologna, the CEIIAV Ethical Committee of Emilia Romagna Regional Health Service, and the National Research Ethics Committee (London, Queen Square, UK), and in line with the Declaration of Helsinki (International Committee of Medical Journal Editors, 1991).

Table 14. Demographic and clinical data of vmPFC patients, control patients, and vmPFC healthy controls.

	N	Gender	Age (years)	Education (years)	Chronicity (years) [range]	SPM	Phonemic fluency	Semantic fluency	Digit span	Corsi test	Prose recall	ROCF copy	ROCF recall
vmPFC patients	8	6 M, 2 F	59.25 (9.38)	10.00 (2.98)	6.75 (5.09) [1-15]	30.28 (4.78)	27.13 (6.53)	43.38 (10.43)	5.34 (0.68)	4.51 (0.80)	9.98 (3.62)	32.97 (5.40)	15.47 (6.84)
Control patients	10	8 M, 2 F	59.10 (10.91)	9.90 (3.84)	1.95 (1.12) [0.5-4]	28.65 (7.05)	34.10 (10.73)	52.60 (11.84)	5.90 (0.74)	4.19 (0.72)	13.16 (4.10)	32.70 (5.67)	17.03 (5.26)
vmPFC healthy controls	10	10 M	57.90 (5.76)	10.00 (2.58)	-	-	-	-	-	-	-	-	-

vmPFC = ventromedial prefrontal cortex; M = male; F = female; SPM = Ravens Standard Progressive Matrices; ROCF = Rey-Osterrieth Complex Figure. Mean corrected scores (in all cases within normal limits), with the standard deviation of the mean in parentheses.

Table 15. Background summary of hippocampal patients and healthy controls from McCormick et al. (2017).

	N	Gender	Age (years)	Chronicity (years) [range]	LHC vol* (mm^3)	RHC vol* (mm^3)	WASI-M (scaled score)	WASI-S (scaled score)	IRM* (z-score)	DRM* (z-score)	RM (z-score)	WM (z-score)
Hippocampal patients	6	6 M	57 (16.9)	6.8 (2.1) [4-9]	2506 (394)	2678 (528)	13.2 (2.2)	12.8 (1.8)	-0.7 (0.8)	-0.7 (0.4)	-0.3 (1.1)	-0.3 (0.8)
Healthy controls	12	12 M	57.2 (16.6)	-	3173 (339)	3286 (301)	13.8 (1.5)	11.8 (2.6)	0.3 (0.3)	0.4 (0.6)	0.1 (0.6)	0.1 (1.1)

Full details are provided in McCormick et al. (2017). Mean scores with standard deviations in parentheses. *Significant difference between the groups. M = male; LHE = left hippocampal volume; RHC = right hippocampal volume; WASI-M = Matrix Reasoning and WASI-S = Similarities subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). z-scores = individual tests have been transformed into z-scores and averaged across patients and controls within specific neuropsychological domain. Therefore, a mean z-score of zero indicates that both groups had the same mean. IRM = immediate recall memory: Wechsler Memory Scale (WMS-III; Wechsler, 1997), logical memory 1 units and thematic scores, wordlist 1 total recall, and Rey-Osterrieth complex figure immediate recall (Osterrieth, 1944). DRM = delayed recall memory: WMS-III logical memory 2 units and thematic scores, and Rey-Osterrieth complex figure delayed recall. RM = recognition memory: Warrington Recognition Memory Test for words and faces (Warrington, 1984), WMS-III wordlist 2 recognition. WM = working memory: WMS-III digit span subtest.

Neuropsychological profile

Table 14 shows the vmPFC and control patients' neuropsychological profile. In general the vmPFC and control patients' cognitive functioning was preserved, as indicated by their scores on the Ravens Standard Progressive Matrices (see Spinnler and Tognoni, 1987, for normative data) and verbal fluency (Spinnler and Tognoni, 1987), which were within the average range for both groups. vmPFC and control patients also had intact verbal and spatial short-term memory, as assessed with the digit span and Corsi tests (Spinnler and Tognoni, 1987), and verbal and spatial long-term memory, as assessed with prose recall and recall of the Rey-Osterrieth complex figure (Spinnler and Tognoni, 1987). The copy of the Rey-Osterrieth complex figure was also normal (Spinnler and Tognoni, 1987). Direct comparison of the vmPFC patients and control patients showed comparable scores in the above neuropsychological tests (p's > 0.10 in all cases). In some cases, control patients with posterior lesions had visual field deficits, including hemianopia (in six cases), quadrantopia (in one case) and neglect (in one case). In these patients, however, the detection of visual stimuli in standardized tests was not impaired when eye movements were allowed (as was the case in the present experiment), and visual search performance was within normal limits (see Supplementary Table S3). We were, therefore, confident that they would be able to perform the possible/impossible scenes task.

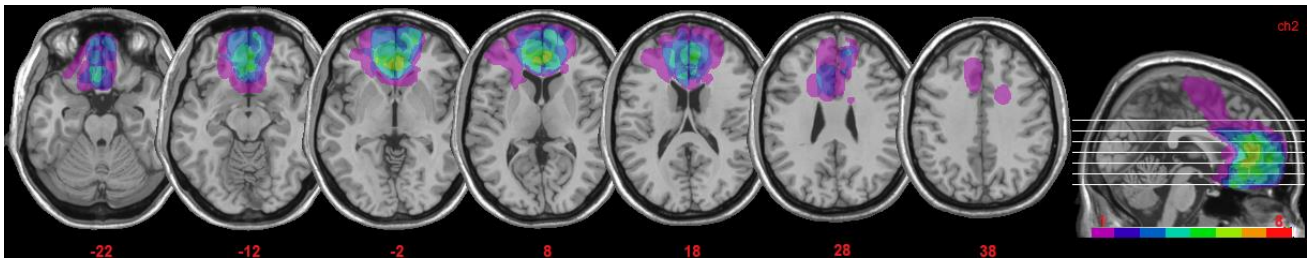
As detailed in McCormick et al. (2017; see also Table 15), the hippocampal patients displayed an impairment in immediate and delayed memory recall, and they recollected significantly fewer episodic, but not semantic, details on the Autobiographical Interview (Levine et al., 2002). There were no significant differences between patients and controls on general cognitive ability – which was above average as measured by tasks such as the Matrix Reasoning subtest of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) – and on a range of neuropsychological tests assessing semantic memory, language, perception, executive functions and mood.

Lesion analysis

vmPFC and control patients' individual lesions, derived from magnetic resonance imaging or computerized tomography images, were manually drawn by an expert neurologist (not involved in the present study, and blind to task performance), or by F.D.L, and then verified by the same neurologist, directly on each slice of the normalized T1-weighted template MRI scan from the Montreal Neurological Institute (Holmes et al., 1998). This template is approximately oriented to match Talairach space (Talairach & Tournoux, 1988) and is distributed with MRIcro (Rorden & Brett, 2000). This manual procedure combines segmentation (identification of lesion boundaries) and registration (to a standard template) into a single step, with no additional transformation required (Kimberg et al., 2007). MRIcro software was used to estimate lesion volumes (in cc) and generate lesion overlap images. Figure 12 shows the extent and overlap of brain lesions in the vmPFC patients. The Brodmann's areas (BA) that were mainly affected were BA 10, BA 11, BA 24, BA 25, BA 32, with the region of maximal overlap occurring in BA 11 (M = 16.22 cc, SD = 10.23), BA 10 (M = 9.42 cc, SD = 7.80), and BA 32 (M = 6.71 cc, SD = 5.22). One vmPFC patient had a very large lesion that extended to dorsal prefrontal cortex (BA 6 and BA 8). Excluding this patient from the analyses, however, did not alter the results. For the control patients, the areas mainly affected were BAs 17-19 (M = 13.77 cc, SD = 19.42), BAs 20-22 and BA 37 (M = 4.49 cc, SD = 10.21) (see Supplementary Figure S3). There was no significant difference in lesion volume between vmPFC patients and control patients (46.27 vs. 24.22 cc, t = 1.74, p = 0.10).

The hippocampal patients had selective bilateral hippocampal damage as confirmed by manual segmentation of the hippocampi and whole-brain grey matter analyses as described in McCormick et al. (2017) and summarized in Table 15.

Figure 12. Lesion overlap in the vmPFC patients. Representative axial slices and cumulative midsagittal views of the standard Montreal Neurological Institute brain showing the extent of lesion overlap in the vmPFC patients. The white horizontal lines on the sagittal view are the positions of the axial slices, and the red numbers below the axial views are the x coordinates of each slice. The colour bar indicates the number of overlapping lesions. Maximal overlap occurred in BA 10, 11 and 32. The left hemisphere is on the left side. See Supporting Figure S1 for lesion overlap in the control patients.



Stimuli

The stimuli were those used in McCormick et al. (2017) – see Figure 13. The images for the main experiment were closely matched between the semantic and the constructive conditions in their format (horizontal: 450 pixels (high) X 600 pixels (wide), vertical: 600 X 450 pixels; on average 10 vertical images per condition, range 8 to 12) and type (e.g., whether they were photographs or paintings; on average 13.5 paintings per condition, range 12 to 14). All images were in color, except one semantic possible scene and one semantic impossible scene. The content of the images was carefully matched across the semantic and constructive conditions (e.g., a possible and an impossible semantic landscape or a possible and an impossible constructive tower).

Procedure

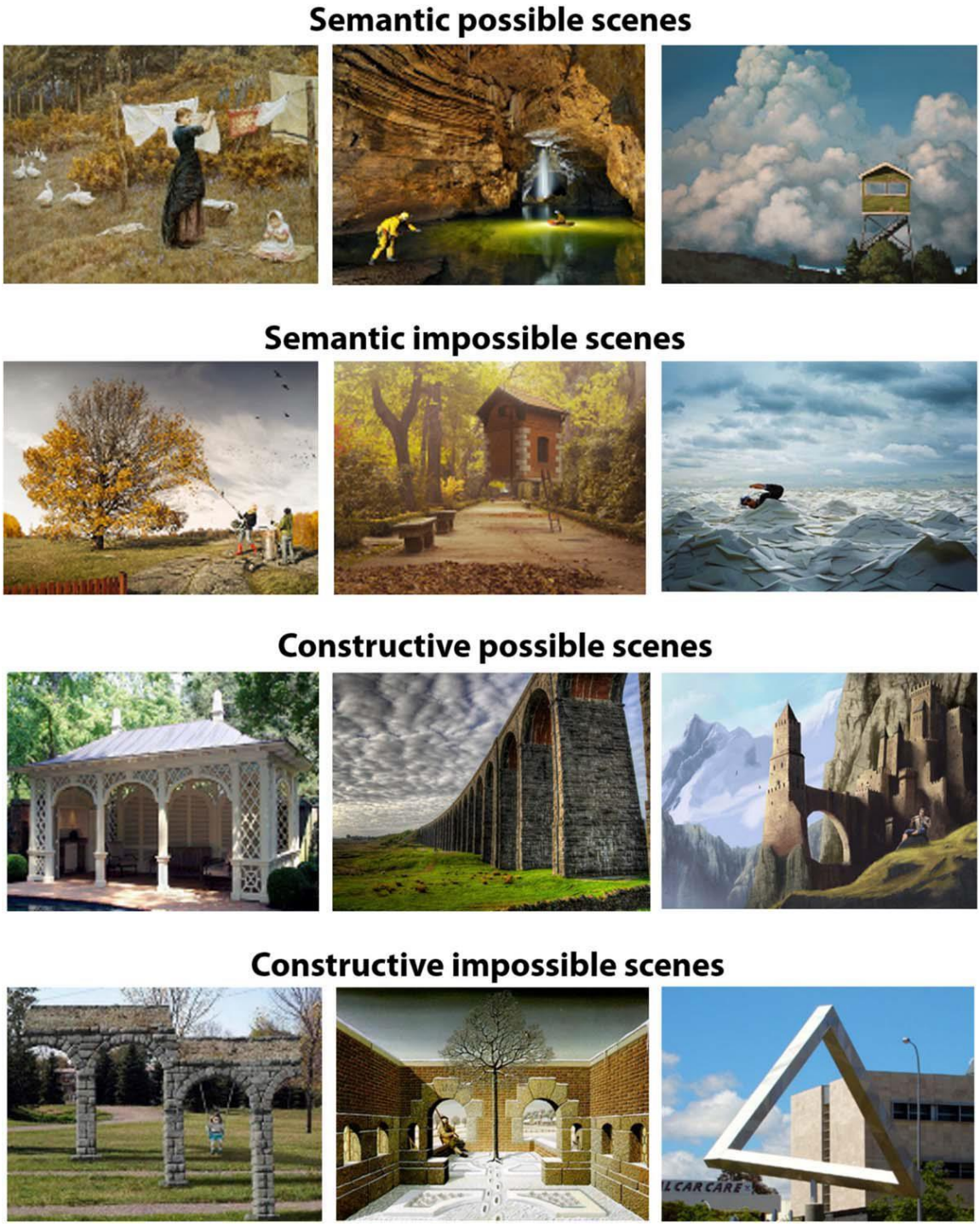
Participants were told that they would be viewing pictures of scenes on a computer screen one at a time and that they should examine these pictures carefully because some of the scenes would depict something impossible that they should detect. First, examples of semantic and constructive violations were shown to the participants, ensuring that they understood what was meant by these errors, with experimenters using various synonyms of the word "impossible" (e.g., "not quite right," "odd," "highly unlikely"). For the semantic violations, the content of an image was wrong in some way (e.g., an elephant with butterfly ears, flying on clouds, breathing under water). For constructive violations, an image depicted a spatially implausible scene (e.g., wrong perspectives, endless staircases). During the task, participants were presented with one scene image at a time and were simply asked to decide whether they thought the current scene depicted something that was possible or impossible in the real world and to indicate their response via a key press. They were not explicitly told whether a picture belonged to the semantic or constructive

condition. Before the main experiment, participants underwent a practice session, comprising eight images (two per condition). Each image was presented for three seconds at the center of the screen, then the question "Is this scene possible or impossible?" appeared underneath it. Participants had up to an additional 20 s to look at the scene image and question, and indicated their decision by pressing either key number 1 (possible) or 3 (impossible). Following each possible/impossible decision, participants were asked to rate how difficult they found it to decide whether a scene was possible or impossible (1 = not difficult at all, 2 = somewhat difficult, 3 = very difficult), and how confident they were in their decision on a rating scale (1 = not confident at all, 2 = somewhat confident, 3 = very confident). They were then prompted to press the space bar to proceed to the next scene image. For both difficulty and confidence ratings, participants had a maximum of 15 seconds to respond. During this practice session, the experimenter provided verbal feedback for each image, explaining the difference between stimuli categories if there were any mistakes in assigning an image to either the possible or impossible category, until the participant comprehended the task instructions.

After the completion of the practice session, participants performed the main task, which was identical to the practice session, but consisted of two blocks each containing 50 images (25 semantic and 25 constructive). The images were presented in pseudo random order so that no more than two images of the same condition were presented consecutively. The experiment was run using Cogent 2000 version 125 (Wellcome Centre for Human Neuroimaging, and Institute of Cognitive Neuroscience, UCL, London, UK). Completion of the practice and main experiment took participants about 50 minutes, including breaks.

Figure 13. Example stimuli from the possible/impossible scenes task. Semantic scenes are presented in the upper two panels. The possible semantic scene depicts a woman hanging up some laundry, whereas the impossible semantic scene below shows a woman vacuuming the leaves from a tree, which would not happen in the real world. The lower two panels depict examples of constructive scenes. On the left side of the panel, a possible constructive scene includes a typical pavilion, whereas an impossible constructive scene beneath shows arches that would not be possible to build in the real world. Specifically, the top connecting structure suggests a flat architecture yet the columns of the arches are located at different depths within the scene.
Impossible scenes were adapted from the following sources:

Semantic: http://www.erikjohanssonphoto.com/; http://www.ucreative.com/inspiration/surreal-photography-of-flying-house-by-rafa-zubiria/; http://www.gettyimages.co.uk/detail/photo/businessman-swimming-in-sea-of-envelopes-high-res-stockphotography/200354836-001;
Constructive: http://www.moillusions.com/funny-lookin-arch-illusion/;
http://impossible.info/english/art/mey/mey3.html;
https://upload.wikimedia.org/wikipedia/commons/3/38/Perth_Impossible_Triangle.jpg.



Data analyses

Given that in all cases the dependent variables were normally distributed (Kolmogorov-Smirnov $d > 0.10$, $p > 0.05$), behavioral data were analyzed with parametric tests. We first

compared vmPFC patients with vmPFC healthy controls and control patients. We also compared the three patient groups directly. In this regard, we were cognizant of the fact that while the vmPFC participants (patients, control patients, healthy controls) were matched on education level and performed within the average range on tests such as the Ravens Standard Progressive Matrices (Spinnler and Tognoni, 1987), the performance of hippocampal patients and their controls was above average on similar tests (e.g. Matrix Reasoning; Wechsler, 1999). Therefore, we made direct comparisons between the three patient groups using z-scores. These were obtained by subtracting each patient's score from the average score of their respective healthy control group (vmPFC healthy controls for vmPFC patients and control patients, and hippocampal healthy controls for hippocampal patients), divided by the standard deviation of the healthy control group. By comparing the z-scores across patient groups in this way, we controlled for differences in general intellectual level.

Comparisons involving three participant groups were analyzed with separate two-way repeated measures analysis of variance (ANOVA) with participant group as a between-subjects factor with three levels (vmPFC patients, control patients, vmPFC healthy controls; or vmPFC, hippocampal and control patients, depending on the analysis), and scene category as a within-subjects factor with two levels (semantic, constructive). Post-hoc comparisons were analyzed with Newman-Keuls tests. All tests were two-tailed, and differences were considered statistically significant at $p < 0.05$.

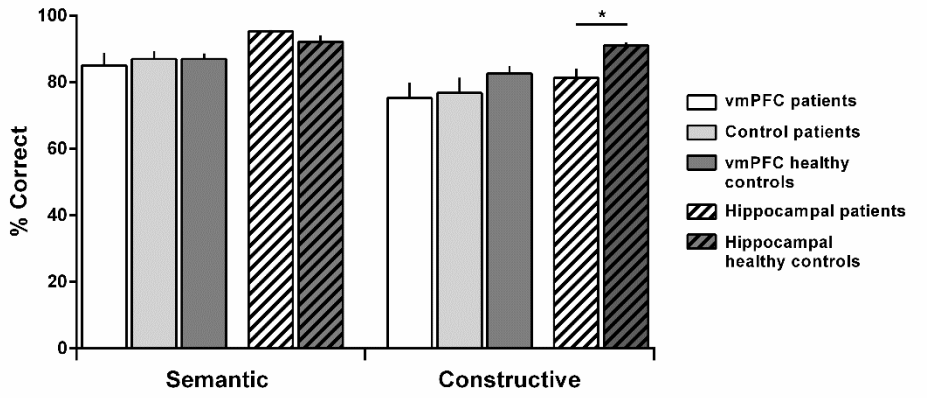
Results

For each of the variables we measured, we first present the results of the comparison between the vmPFC patients, the control patients and their healthy controls. We then report the direct comparison of the vmPFC patients, the control patients and McCormick et al.'s (2017) hippocampal patients.

Accuracy

We first examined the accuracy data for the vmPFC patients, the control patients and their healthy controls (Figure 14; see also Supplementary Figure S4). The ANOVA run on the frequency of correct responses for the two scene categories (semantic, constructive) did not show a significant main effect of group [$F_{(2,25)} = 0.68$, $p = 0.52$] or an interaction between participant group and scene category [$F_{(2,25)} = 0.93$, $p = 0.41$]. We observed a significant main effect of scene category [$F_{(1,25)} = 16.78$, $p < 0.001$], reflecting higher accuracy for semantic compared to constructive scenes across groups ($p < 0.001$). Overall, these results indicate that vmPFC patients were not impaired at detecting semantic or constructive violations compared to their healthy controls. This was also the case for control patients who had damage outside of the vmPFC. Thus, brain damage per se is not sufficient to cause a deficit in identifying impossibilities in scenes. However, as reported by McCormick et al. (2017), hippocampal damaged patients were impaired on this task (also shown in Figure 14 for convenience), specifically in terms of detecting constructive impossibilities.

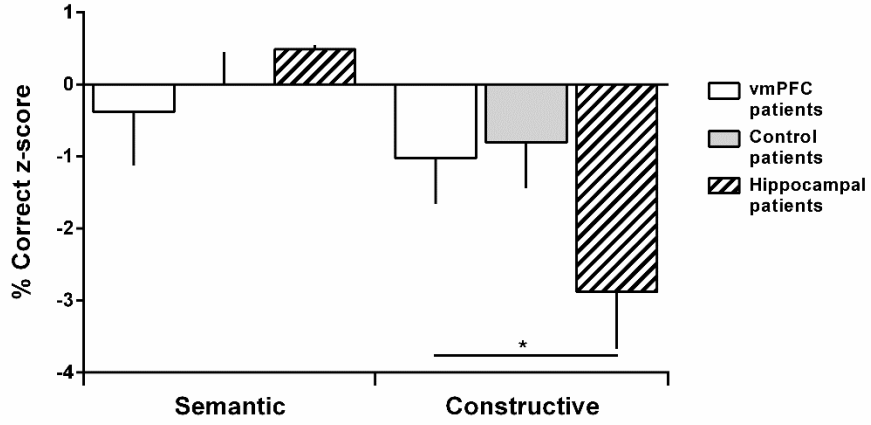
Figure 14. Accuracy results for all participants groups. Mean accuracy raw scores by participant group for the two scene conditions (semantic, constructive). The data and significance levels contrasting patients with hippocampal damage and their healthy controls are from McCormick et al. (2017). Bars represent standard errors of the mean. *p < 0.05.



To compare accuracy directly across vmPFC patients, control patients and hippocampal patients, we conducted an ANOVA on the transformed (z-scores) correct responses, with participant group (vmPFC patients, control patients and hippocampal patients) and scene category (semantic, constructive) as factors (Figure 15; see also Supplementary Figure S5). This showed no significant

effect of participant group [$F_{(2,21)} = 0.56$, $p = 0.58$], but a significant effect of scene category [$F_{(1,21)} = 15.81$, $p < 0.001$], which was qualified by a significant interaction between participant group and scene category [$F_{(2,21)} = 4.17$, $p = 0.03$]. Post-hoc tests revealed that hippocampal patients had lower accuracy for constructive scenes compared to vmPFC patients ($p = 0.04$) and, marginally, control patients ($p = 0.06$), whereas there was no difference between vmPFC and control patients ($p = 0.81$). In contrast, accuracy for semantic scenes was comparable across the three patient groups (p's > 0.59 in all comparisons). Furthermore, hippocampal patients exhibited a lower accuracy for constructive compared to semantic scenes ($p < 0.01$), whereas vmPFC and control patients reported a comparable level of accuracy across scene categories ($p = 0.63$ and $p = 0.49$, respectively).

Figure 15. Accuracy – comparison of the three patient groups. Mean accuracy z-scores for the three patient groups for the two scene conditions. Bars represent standard errors of the mean. *p < 0.05.



Reaction times

Table 16 (see also Supplementary Table S4) shows mean reaction times (RTs) by participant group. The ANOVA on RTs with participant group (vmPFC patients, control patients and vmPFC healthy controls) and scene category (semantic, constructive) as factors did not show a significant main effect of group [$F_{(2,25)} = 0.56$, $p = 0.58$] or a significant interaction between participant group and scene category [$F_{(2,25)} = 0.92$, $p = 0.41$]. We found a significant main effect of scene category [$F_{(1,25)} = 44.68$, $p < 0.0001$], with all participants being faster at judging semantic compared to constructive scenes ($p < 0.001$).

Table 16. Reaction times, difficulty and confidence ratings on the possible/impossible scenes task by participant group and scene category (semantic, constructive).

		RTs (sec)	RTs z-scores	Difficulty	Difficulty z-scores	Confidence	Confidence z-scores
vmPFC patients	Semantic Constructive	7.1 (3.0) 8.5 (1.4)	1.4 (2.3) 0.6 (0.9)	1.2 (0.4) 1.3 (0.3)	0.2 (2.4) -0.1 (1.2)	2.7 (0.3) 2.6 (0.3)	-3.7 (5.1) -3.2 (3.1)
Control patients	Semantic Constructive	6.3 (4.0) 8.4 (4.3)	0.8 (3.0) 0.5 (2.7)	1.2 (0.2) 1.4 (0.3)	0.0 (1.0) 0.3 (1.0)	2.8 (0.1) 2.6 (0.3)	-2.2 (2.6) -2.7 (3.0)
vmPFC healthy controls	Semantic Constructive	5.3 (1.3) 7.6 (1.6)	-- --	1.2 (0.2) 1.4 (0.3)	-- --	2.9 (0.1) 2.9 (0.1)	-- --
Hippocampal patients	Semantic Constructive	6.6 (1.4) 7.3 (1.0)	-0.1 (0.6) 0.1 (0.4)	1.1 (0.1) 1.3 (0.1)	-0.6 (0.5) -0.7 (0.4)	2.8 (0.1) 2.7 (0.2)	0.1 (0.9) 0.2 (0.9)
Hippocampal healthy controls	Semantic Constructive	6.7 (2.2) 7.1 (2.3)	-- --	1.3 (0.2) 1.4 (0.3)	-- --	2.8 (0.1) 2.7 (0.2)	-- --

Notes. vmPFC = ventromedial prefrontal cortex. For all groups, means are displayed with standard deviations in parentheses. RT = reaction times, calculated from the onset of the 'possible/impossible' question; sec = seconds. Difficulty and confidence ratings ranged from 1 (not at all) to 3 (very difficult/confident). Z-scores were calculated by subtracting the mean score of their respective healthy control group from each patient's score, divided by the standard deviation of the respective healthy control group.

Direct comparison of the three patients groups using an ANOVA on z-scores for RTs (Table 16) with participant group (vmPFC patients, control patients, hippocampal patients) and scene category (semantic, constructive) as factors did not show any significant effect of group [$F_{(2,21)}$ = 0.38, p = 0.69], scene category [$F_{(1,21)}$ = 1.42, p = 0.25] or participant group x scene category interaction [$F_{(2,21)}$ = 1.16, p = 0.33].

Difficulty

Mean difficulty ratings are shown on Table 16 (see also Supplementary Table S4). The ANOVA conducted on difficulty scores with participant group (vmPFC patients, control patients and vmPFC healthy controls) and scene category (semantic, constructive) did not show a significant main effect of group [$F_{(2,25)}$ = 0.06, p = 0.94] or a significant interaction between participant group and scene category [$F_{(2,25)}$ = 2.13, p = 0.14]. We found a significant main effect of scene category [$F_{(1,25)}$ = 33.81, p < 0.0001], with all participants judging processing semantic (versus constructive) scenes as less difficult (p < 0.001).

Direct comparison of the three patients groups using an ANOVA on z-scores for the difficulty rating with participant group (vmPFC patients, control patients, hippocampal patients)

and scene category (semantic, constructive) as factors did not show any significant effect of group [$F_{(2,20)}$ = 0.68, p = 0.52], scene category [$F_{(1,20)}$ = 0.00, p = 1.00] or participant group x scene category interaction [$F_{(2,20)}$ = 1.04, p = 0.37].

Confidence

Mean confidence ratings are shown on Table 16 (see also Supplementary Table S4). The ANOVA conducted on confidence scores with group (vmPFC patients, control patients and vmPFC healthy controls) and scene category (semantic, constructive) as factors showed significant main effects of group [$F_{(2,25)}$ = 3.95, p = 0.03] and scene category [$F_{(1,25)}$ = 42.20, p < 0.0001], qualified by a significant participant group x scene category interaction [$F_{(2,25)}$ = 3.59, p = 0.04]. Post-hoc tests revealed that vmPFC patients (p = 0.03) and, marginally, control patients (p = 0.06) were less confident than vmPFC healthy controls in their decisions for constructive scenes, but not for semantic scenes (p's > 0.19 in both cases). There were no differences between vmPFC patients and control patients in confidence for either semantic or constructive scenes (all p's > 0.39). Furthermore, both vmPFC and control patients were less confident in their decisions for constructive compared to semantic scenes (in both cases, p < 0.001), whereas vmPFC healthy controls reported a comparable level of confidence across the two categories (p = 0.08).

Comparing the three patient groups directly using an ANOVA on z-scores for the confidence ratings with participant group (vmPFC patients, control patients, hippocampal patients) and scene category (semantic, constructive) as factors did not show any significant effect of group [$F_{(2,20)}$ = 2.14, p = 0.14], scene category [F(1,20) = 0.03, p = 0.87] or participant group x scene category interaction [$F_{(2,20)}$ = 1.03, p = 0.38].

Discussion

In this study we investigated the contribution of the vmPFC to different aspects of scene processing by asking patients with bilateral vmPFC lesions to detect either semantic or constructive violations ('impossibilities') in naturalistic scenes. We found no evidence for statistically significant

differences between the vmPFC patients, brain damaged control patients and healthy controls in the accuracy of their performance, their reaction times or the perceived difficulty of the tasks. This suggests that, as predicted, vmPFC patients could process these scenes, even where an internal scene model is thought to be required, as in the case of the constructive scenes. The similar performance of the vmPFC patients for semantic and constructive scenes, and the analogous data from the brain-damaged control patients, suggests that the vmPFC may not play a specific role in scene processing, at least as it was tested here. This result is in contrast to the hippocampal patients reported by McCormick et al. (2017) on the same task, who could detect semantic violations but had a deficit in detecting constructive violations relative to their healthy controls. This suggests an imbalance in semantic and constructive scene processing in such patients that speaks to a specific role for the hippocampus in scene construction.

Before discussing these results further, it is prudent to consider some methodological points. The vmPFC patients, their patient controls and healthy controls were all closely matched to each other in terms of demographic variables. This was also true for the hippocampal patients and their healthy controls. However, while being matched in terms of age, the three vmPFC-related groups were not comparable to the two hippocampal-related groups in terms of general intellectual functioning, with the hippocampal groups scoring above average. The fact that the three vmPFC-related groups scored similarly on all of the tasks but overall scored lower than the two hippocampal-related groups may be associated with this point, suggesting that the possible/impossible scenes task is affected by factors such as education. Indeed, an example of this is when one vmPFC healthy control participant was suspicious when he was shown a picture of the northern lights. He (wrongly) concluded that the scene was impossible because he reasoned that in nature one never sees a green sky. While we acknowledge that it would be preferable to match all patients and controls in terms of education and general intellectual level, the patients in question are so rare that one has to test whatever patients are available. It is therefore important, as we have done here, to examine each patient group versus the relevant healthy control group first, and then use

these transformed scores when comparing the patient groups directly. In this context, we found that there were no differences between vmPFC, control and hippocampal patients in their accuracy in detecting semantic violations in scenes, reaction times, perceived task difficulty, and confidence. The only difference was the hippocampal patients being impaired at detecting constructive violations in scenes. This was not the case for the other patient groups, even the control patients who had occipital lesions and hemianopias.

Although apparently at odds with extant studies that reported a scene construction impairment in patients with vmPFC damage (Bertossi, Aleo, et al., 2016; Bertossi, Tesini, Cappelli, & Ciaramelli, 2016; Bertossi, Candela, De Luca, & Ciaramelli, 2017; De Luca et al., 2018), in fact our finding of vmPFC patients' preserved detection of semantic and constructive violations in scenes helps to specify more precisely the role of the vmPFC in scene imagery. Moreover, these results highlight differences in the respective contributions of the vmPFC and hippocampus to scene processing. The standard scene construction task requires the imagination of scenes (Hassabis, Kumaran, Vann, & Maguire, 2007), and although cues are provided, it is still relatively unconstrained, much as is imagining what might be beyond the view in scenes (Mullally, Intraub, & Maguire, 2012; De Luca et al., 2018) and the free recall of autobiographical memories (Bertossi, Tesini, et al., 2016). vmPFC patients are impaired on all of these tasks. However, they can describe specifically cued snapshot scenes from autobiographical memories (Kurczek et al., 2015). As we have shown here, vmPFC patients can detect constructive violations in scenes, which is known to provoke the formation of internal scene models in healthy controls (McCormick et al., 2017). This is because in order to detect a constructive violation, one has to visualise how the correct scene would look, and then use this internal scene model to compare to the scene stimulus. This is not necessary for detecting semantic violations in scenes, which involves instead the retrieval of congruent abstract knowledge of the world, necessary to understand semantic relationships between elements of the scene and infer its meaning, rather than the construction of an internal model of the scene (McCormick et al., 2017). Our findings are, therefore, concordant with the idea that vmPFC

patients have an intact ability to construct scene imagery when everything they need to perform a task is in front of them, and any requirement for endogenous, self-initiating processing (such as the need to construct an internal scene model) is cued (McCormick, Ciaramelli, De Luca, & Maguire, 2018).

Hippocampal patients, on the other hand, seem to have a fundamental deficit in the formation of scene imagery (Hassabis, Kumaran, Vann, & Maguire, 2007; Race, Keane, & Verfaellie, 2011; Mullally, Intraub, & Maguire, 2012; Kurczek et al., 2015; De Luca et al., 2018). For example, in the scene construction task, they could generate appropriate details that would be associated with a scene, but they were unable to incorporate this information into spatially coherent scene imagery of the type required to detect constructive violations in the task we report here.

The contrasting problems faced by vmPFC and hippocampal patients are evident not just in the current tasks and in a mnemonic context, but are manifest across cognition. In our review (McCormick, Ciaramelli, et al., 2018), we discuss this in detail, but one example illustrates this point clearly. We all engage in mind-wandering, where we mentally decouple from the external world and focus on endogenous processing (Antrobus, Singer, & Greenberg, 1966; Smallwood & Schooler, 2006; Smallwood & Schooler, 2015). vmPFC patients have been found to mind-wander much less than matched healthy controls (Bertossi & Ciaramelli, 2016), and seemed to have difficulty directing their attention inwards. Hippocampal patients mind-wandered as much as matched healthy controls, so had no difficulty focusing their attention inwards (McCormick, Rosenthal, Miller, & Maguire, 2018). However, whereas controls thought about the past, present and future, imagining vivid visual scenes, hippocampal damage resulted in thoughts primarily about the present comprising verbally-mediated semantic knowledge. Thus, while vmPFC and hippocampal patients seem to share many of the same deficits, the underlying reasons may be different. Unlike hippocampal patients, vmPFC patients do not seem to initiate endogenous processing related to the accessing, filtering and curating of the contents of cognition. However, when the need for such processing is circumvented, because the presentation of a test item provides

a highly specific cue as to which internal model of a scene to activate, as in our possible/impossible scenes task here, then a deficit is no longer apparent.

While we have largely focussed so far on the constructive scene task, it also interesting that the vmPFC patients correctly and quickly identified semantic impossibilities in scenes. The vmPFC has been linked with retrieval (Cabeza & Nyberg, 1997; Cabeza & Nyberg, 2000) or selection (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997) of information from semantic memory. BA 11 and 47 are active during categorisation (Jennings, McIntosh, Kapur, Tulving, & Houle, 1997) and generation (Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995) of words, lexical decisions about abstract versus concrete words (Binder, Westbury, & McKiernan, 2005), processing of famous faces and names (Gorno-Tempini et al., 1998; Woodard et al., 2007) and the semantic recall of object representations (Assaf et al., 2006). Therefore, vmPFC is considered one of the three main brain areas specialised for storage and retrieval of semantic knowledge, along with posterior heteromodal association cortex (angular gyrus, middle temporal gyrus and fusiform gyrus) and lateral temporal cortices (Binder et al., 2009; Chadwick et al., 2016; McAndrews, Girard, Wilkins, & McCormick, 2016).

In line with these findings, it has been proposed that the vmPFC might instantiate superordinate knowledge structures that reflect abstracted commonalities across multiple experiences – so called schemas (Ghosh & Gilboa, 2014; Gilboa & Marlatte, 2017). The vmPFC is thought to activate context-relevant schemas that are used to guide memory retrieval or store new information (Gilboa et al., 2006; Warren, Jones, Duff, & Tranel, 2014; Gilboa & Marlatte, 2017), playing a crucial role in memory formation and integration (Van Kesteren, Ruiter, Fernandez, & Henson, 2012; Schlichting & Preston, 2015). The discrimination between possible and impossible semantic scenes could require the re-activation of memory schemas congruent with the observed scene in order to understand what is typical in a given scenario. However, the vmPFC patients in the present study easily distinguished between possible and impossible semantic scenes, and correctly felt what was right or wrong in a scene. This may speak against a schema account of

vmPFC, or at least call for a specification of what aspect of a schema is supported by vmPFC (the knowledge of schema-congruent elements, or of the 'scripts' that prescribe the appropriate transitions between different aspects of experiences, etc.) to be investigated in future studies. It is also possible, however, that the semantic scene impossibilities were sufficiently obvious to be identified without requiring reinstatement of detailed knowledge-based schemas, or that schema-related (Ghosh et al., 2009) and feeling of rightness deficits (Gilboa et al., 2006) are only observable in vmPFC patients with confabulation, which was not present in the vmPFC patients tested here.

In conclusion, we have shown that patients with damage to the vmPFC can identify both constructive and semantic violations in scenes, in contrast to patients with focal hippocampal lesions, who were selectively impaired at detecting constructive scene impossibilities. These findings suggest that vmPFC patients can accurately perceive scenes, appreciate their spatial-constructive nature, extract meaning and make semantic judgements about them in the presence of very specific cues (in this case the scene stimuli themselves). However, they might be particularly impaired during unconstrained tasks that have the requirement for selecting appropriate mental representations or responses, inhibiting those that are competing but irrelevant, using schematic knowledge as a guide (McCormick, Ciaramelli, De Luca, & Maguire, 2018).

Supplementary Table S3. Mean percentage of accurate responses in visual detection and visual search tasks (Bolognini, Rasi, Coccia, & Làdavas, 2005; Passamonti, Bertini, & Làdavas, 2009) for control patients with hemianopia (N = 8).

Test	**Visual detection: eye movements not allowed**		**Visual detection: eye movements allowed**		**Visual search: letters**	**Visual search: numbers**
	R	**L**	**R**	**L**		
Control patients with left hemisphere lesions (N = 4)	64*	92	88	97	100	100
Control patients with right hemisphere lesions (N = 3) §	97	81	99	89	96	100

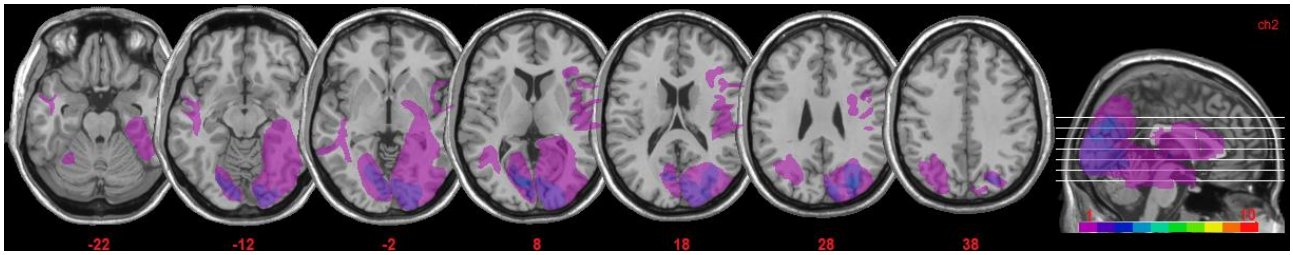
Notes. R = right hemifield, L = left hemifield. The visual detection and search tasks are from Bolognini et al., 2005. Asterisks highlight a pathological performance. The performance is considered within the normal range if it reaches 80% accuracy. § Visual detection test data are missing for one of the four hemianopic patients with a left hemisphere lesion.

Supplementary Table S4. Reaction times, difficulty and confidence ratings on the possible/impossible scenes task by participant group decomposed into four scene categories.

		RTs (sec)	**RTs z-scores**	**Difficulty**	**Confidence**	**Difficulty z-scores**	**Confidence z-scores**
vmPFC patients	Semantic possible	7.8 (2.3)	0.2 (1.1)	1.2 (0.3)	2.7 (0.3)	-0.3 (1.2)	-2.7 (3.7)
	Semantic impossible	6.5 (4.3)	2.6 (3.5)	1.3 (0.4)	2.8 (0.3)	1.2 (3.9)	-4.1 (6.2)
	Constructive possible	8.9 (1.9)	0.2 (0.8)	1.3 (0.3)	2.6 (0.3)	-0.2 (1.0)	-2.7 (2.6)
	Constructive impossible	8.1 (2.5)	0.7 (1.3)	1.4 (0.3)	2.5 (0.4)	0.0 (1.5)	-2.7 (3.3)
Control patients	Possible semantic	7.4 (4.3)	0.1 (2.0)	1.3 (0.2)	2.8 (0.2)	-0.2 (0.7)	-1.4 (2.0)
	Impossible semantic	5.2 (4.4)	1.6 (3.6)	1.2 (0.2)	2.9 (0.2)	0.3 (1.6)	-2.5 (3.7)
	Possible constructive	8.8 (4.1)	0.1 (1.7)	1.5 (0.2)	2.6 (0.3)	0.3 (0.8)	-2.3 (2.3)
	Impossible constructive	8.1 (4.8)	0.7 (2.4)	1.4 (0.3)	2.6 (0.4)	0.2 (1.2)	-2.3 (3.5)
vmPFC healthy controls	Possible semantic	7.3 (2.2)	--	1.3 (0.3)	2.9 (0.1)	--	--
	Impossible semantic	3.3 (1.2)	--	1.1 (0.1)	3.0 (0.0)	--	--
	Possible constructive	8.5 (2.4)	--	1.4 (0.3)	2.9 (0.1)	--	--
	Impossible constructive	6.7 (2.0)	--	1.4 (0.2)	2.8 (0.1)	--	--
Hippocampal patients	Possible semantic	7.2 (2.1)	0.1 (0.9)	1.2 (0.2)	2.8 (0.2)	-0.6 (0.9)	-0.1 (0.8)
	Impossible semantic	5.9 (1.5)	-0.2 (0.6)	1.1 (0.1)	2.8 (0.2)	-0.4 (0.4)	0.2 (0.8)
	Possible constructive	7.6 (1.6)	0.1 (0.5)	1.3 (0.2)	2.7 (0.2)	-0.4 (0.7)	0.1 (0.9)
	Impossible constructive	7.0 (1.3)	0.1 (0.7)	1.2 (0.2)	2.8 (0.2)	-0.9 (0.9)	0.2 (1.0)
Hippocampal healthy controls	Possible semantic	7.0 (2.4)	--	1.3 (0.2)	2.8 (0.2)	--	--
	Impossible semantic	6.4 (2.3)	--	1.2 (0.3)	2.8 (0.2)	--	--
	Possible constructive	7.3 (3.1)	--	1.5 (0.3)	2.7 (0.2)	--	--
	Impossible constructive	6.9 (1.8)	--	1.4 (0.2)	2.7 (0.2)	--	--

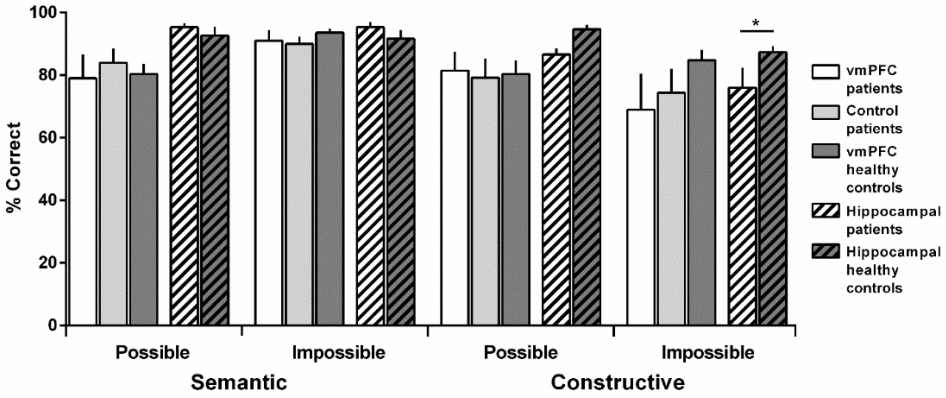
Notes. vmPFC = ventromedial prefrontal cortex. For all groups, means are displayed with standard deviations in parentheses. RT = reaction times, calculated from the onset of the 'possible/impossible' question; sec = seconds. Difficulty and confidence ratings ranged from 1 (not at all) to 3 (very difficult/confident). Z-scores were calculated by subtracting the mean score of their respective healthy control group from each patient's score, divided by the standard deviation of the respective healthy control group.

Supplementary Figure S3



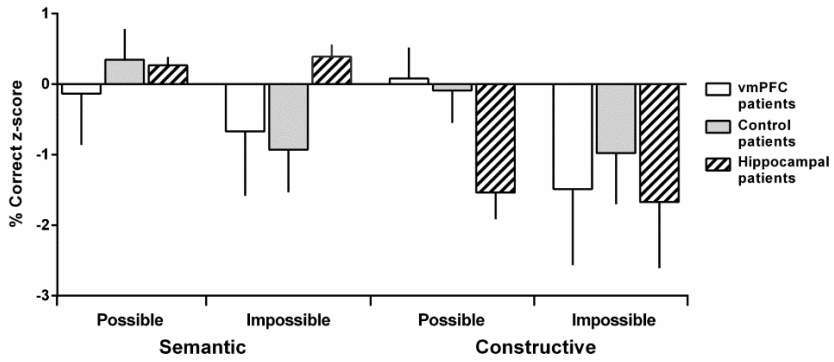
Extent and overlap of brain lesions for the control patients. The figure represents the patients' lesions projected on the same six axial slices of the standard Montreal Neurological Institute brain as shown in Figure 1. The white horizontal lines on the sagittal view are the positions of the axial slices, and the red numbers below the axial views are the z coordinates of each slice. The color bar indicates the number of overlapping lesions. Maximal overlap occurred in BA's 17-19, 37. The left hemisphere is on the left side.

Supplementary Figure S4



Mean accuracy raw scores by participant group for the tasks when decomposed into four scene categories (semantic possible, semantic impossible, constructive possible, and constructive impossible). The data and significance level (*$p < 0.05$) contrasting patients with hippocampal damage and their controls are from on McCormick et al. (2017). Bars represent standard errors of the mean.

Supplementary Figure S5



Mean accuracy z-scores for the three patient groups for the tasks when decomposed into four scene categories (semantic possible, semantic impossible, constructive possible, constructive impossible).

Chapter 4.

Episodic future thinking reduces delay discounting in patients with vmPFC damage

In this chapter, I will come back to one specific form of mental event construction, episodic future thinking, and study its relation and possible contribution to decision making. I will investigate whether promoting episodic future thinking in vmPFC patients reduces their delay discounting rates, and suggest a role for vmPFC in guiding future-oriented choice.

Study 5. Episodic cueing decreases delay discounting in patients with vmPFC damage.

co-authored with Elisa Ciaramelli, Donna Kwan, Francesca Bianconi, Violetta Knyagnytska, Carl Craver, Leonard Green, Joel Myerson, R. Shayna Rosenbaum (*in preparation*).

Introduction

Choices are often intertemporal, requiring a tradeoff of short-term and long-term outcomes (e.g., should I smoke this cigarette or think about my health instead?). Humans, and even non-human animals (Ainslie, 1975; Rosati, Stevens, Hare, & Hauser, 2007), tend to prefer immediate over delayed rewards, even when waiting would yield larger payoffs. This phenomenon reflects the decrease in subjective value of a reward as the delay until its receipt increases, known as delay discounting (DD) (Ainslie, 1975; Myerson & Green, 1995). A range of clinical conditions (e.g., drug addiction, compulsive gambling, obesity) are associated with increased DD, reflecting the inability to forgo immediate gratification to pursue long-term goals of larger value (see Bickel, Koffarnus, Moody, & Wilson, 2014 for a review).

The vmPFC is engaged during intertemporal choices (McClure, Laibson, Loewenstein, & Cohen, 2004; Kable & Glimcher, 2007), and plays a necessary role in the valuation of future rewards. Patients with damage to vmPFC (Sellitto, Ciaramelli, & di Pellegrino, 2010; Peters & D'Esposito, 2016), as well as animals with lesions in homologous regions (Winstanley, Theobald,

Cardinal, & Robbins, 2004; Rudebeck, Walton, Smyth, Bannerman, & Rushworth, 2006), indeed show increased DD, a disproportionate prioritization of smaller, immediate rewards over larger, future rewards, which is associated with poor self-control and impulsivity. Additional aspects of vmPFC patients' clinical presentation are indicative of 'myopia for the future' (Bechara, Damasio, Damasio, & Anderson, 1994): vmPFC patients conceive future events that are closer in time (Fellows & Farah, 2005) and poorer in detail compared to those imagined by healthy and brain-damaged controls (Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016; Bertossi, Tesini, Cappelli, & Ciaramelli, 2016; Bertossi, Candela, De Luca, & Ciaramelli, 2017), and tend not to think about their future spontaneously (Bertossi & Ciaramelli, 2016).

Here we test the possibility that individuals who show atypical DD as a result of focal lesions to vmPFC recover performance if provided with structure in the form of specific, personally meaningful event cues. Recent research has shown that episodic future thinking (Suddendorf & Corballis, 1997; Atance & O'Neill, 2001), the mental simulation of events relevant to one's own future, can reduce DD. Peters and Büchel (2010) compared a standard DD task with an modified task in which personally future events imagined at given delays were provided as cues during choices involving rewards available at those delays. In the episodic cueing (compared to the standard) task, individuals' preferences shifted towards future rewards, and the strength of this effect was associated with the vividness of the imagined future event, and with increased functional coupling between the hippocampus and medial prefrontal regions typically associated with reward processing (Peters & Büchel, 2010; Benoit, Gilbert, & Burgess, 2011). The effect of episodic cueing on DD is consistently found in healthy adults (Peters & Büchel, 2010; Benoit, Gilbert, & Burgess, 2011; Liu, Feng, Chen, & Li, 2013; Lin & Epstein, 2014), as well as in patients with substance abuse disorders (Daniel, Stanton, & Epstein, 2013; Snider, LaConte, & Bickel, 2016), in whom it extends to real-world indices of impulsive choice, such as impulsive drinking or eating.

The present study investigates whether episodic cueing can reduce DD in patients with vmPFC damage. Such a finding would be important for both theoretical and practical reasons.

vmPFC patients have impaired episodic future thinking (as well as episodic remembering) (Bertossi, Tesini, et al., 2016), just as amnesic patients with medial temporal lobe (MTL) lesions, including the hippocampus (Race, Keane, & Verfaellie, 2011; Race, Keane, & Verfaellie, 2013), consistent with the finding that vmPFC and the MTL are both part of a core network of brain regions mediating episodic simulation (Addis, Wong, & Schacter, 2007; Botzung, Denkova, & Manning, 2008). The fact that vmPFC patients have an episodic future thinking impairment (Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016; Bertossi, Tesini, Cappelli, & Ciaramelli, 2016) that is similar to that observed in patients with MTL lesions may, in itself, limit the efficacy of episodic cueing, because patients may fail to create vivid episodic details to guide DD. Indeed, Palombo et al. (2015) found no effect of episodic cueing on DD in amnesic patients with MTL damage, who also have impaired episodic future thinking. In a similar study, Kwan et al. (2015) found that amnesic patients with impaired episodic future thinking can modulate DD through episodic cueing, though not as much as controls, and that amnesic patients with severe memory problems benefited the least from episodic memory cueing. Considering the similarity of the episodic future thinking impairment between vmPFC and MTL patients, one could expect similar findings in vmPFC patients regarding their ability to benefit from the episodic cueing.

Another possibility, however, is that, unlike in MTL amnesics, episodic future thinking deficit in vmPFC patients is due to impaired strategic retrieval processes, e.g., the instantiation of schemas within which to anchor details for event construction or monitoring of the content of retrieval (Ghosh, Moscovitch, Melo Colella, & Gilboa, 2014; Hebscher & Gilboa, 2016; McCormick, Ciaramelli, De Luca, & Maguire, 2018). If vmPFC patients' difficulty in imagining future episodes, unlike the one observed in hippocampal patients, is due to an inability to initiate endogenous processing necessary to retrieve and monitor the information used to make decisions, then abnormal DD should become less steep with the provision of structure cueing to concrete future events. Lastly, that episodic cues may have modulatory, and possibly remedial, effects on

delay discounting is of clinical importance in understanding future decision-making and in managing its consequences in vmPFC patients.

Methods

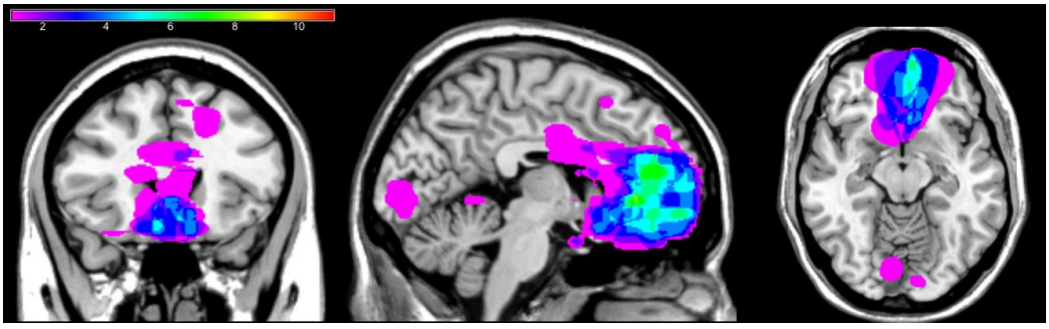
Participants

Thirteen individuals with damage to the vmPFC and 41 age-matched healthy individuals participated in the study. Patients were recruited at the Centre for Studies and Research in Cognitive Neuroscience, Cesena, Italy (5 cases), and at the Rotman Research Institute, Baycrest Health Sciences, Toronto, Canada (8 cases). Patients were selected on the basis of the location of their lesion evident on magnetic resonance imaging (MRI) or computed tomography (CT) scans. Included patients had a lesion in vmPFC, and no other diagnosis likely to affect cognition or interfere with the participation in the study (e.g., psychiatric or cerebrovascular disease, alcohol abuse). In all cases, the lesion was the result of the rupture of an aneurysm of the anterior communicating artery (ACoA), and bilateral. All patients were in the stable phase of recovery (at least 12 months post-lesion).

The boundary of the lesion was manually delineated on each MRI/CT scan using the software MRIcro (Holmes et al., 1998). Figure 16 shows the extent of damage for each patient. The Brodmann's areas (BA) that were mainly affected were BAs 10, 11, and 32. A vmPFC patient had a very large lesion that extended to dorsal prefrontal cortex (BA 6 and BA 8). Excluding these patients from the analyses, however, did not alter the results. vmPFC patients' general cognitive functioning was generally preserved, as indicated by their scores on the Raven Standard Progressive Matrices (see Spinnler & Tognoni, 1987, for normative data). vmPFC performance on standardized tests of attention, executive functions, verbal and spatial short-term memory, and verbal and spatial long-term memory were within the normal range as well (see Spinnler & Tognoni, 1987; Culbertson & Zillmer, 2000; only one out of five Italian vmPFC patients reported a pathological score on this last test).

The eight Canadian patients (4 males, mean age: 59, range 49-76; mean years of education: 15, range: 10-20) were matched to fourteen Canadian healthy individuals (8 males; mean age: 67, range: 55-78; mean years of education: 15, range: 12-20) on education ($t = 0.02$, $p = 0.99$) and gender balance ($\chi^2 = 0.10$, $p = 0.75$). The five Italian patients (all males, mean age: 57, range 46-73; mean years of education: 9, range: 5-13) were matched to 27 healthy Italian individuals (all males; mean age: 58, range: 49-64; mean years of education: 12, range: 8-13) on age ($t = 0.27$, $p = 0.79$) and gender balance ($\chi^2 = 0.00$, $p = 1.00$). In the Italian sample, education was slightly higher in controls than in patients. Participants were screened for clinically significant depression, alcohol and drug abuse, epilepsy, and any other known neurological conditions. The ratio of patients to healthy controls was similar for the Italian and Canadian sample, $\chi^2 = 3.07$, $p = 0.08$. For analysis purposes, we collapsed Italian and Canadian participants into one group of thirteen vmPFC patients (9 males), with a mean age of 59 years (range 46-76) and a mean education of 13 years (range 5-20), and one group of 41 healthy controls (35 males), with a mean age of 61 years (range 49-78) and a mean education of 13 years (range 8-20). vmPFC patients and controls did not differ in age ($t = 1.08$, $p = 0.28$), education ($t = 0.51$, $p = 0.61$), and gender balance ($\chi^2 = 1.70$, $p = 0.19$). All participants gave informed consent, and the study procedures were approved by the ethics committees of the University of Bologna, Baycrest Hospital, and York University, in line with the Declaration of Helsinki (International Committee of Medical Journal Editors, 1991).

Figure 16. Location and overlap of brain lesions. The panel shows the lesions of 10 out of 13 patients with vmPFC damage projected on the same seven axial slices and on the mesial view of the standard Montreal Neurological Institute brain. The level of the axial slices has been marked by white horizontal lines on the mesial view of the brain. *z*-coordinates of each axial slice are given. The color bar indicates the number of overlapping lesions. In each axial slice, the left hemisphere is on the left side. Maximal overlap occurs in the medial frontal cortex (BAs 10,11,32).



Delay discounting task

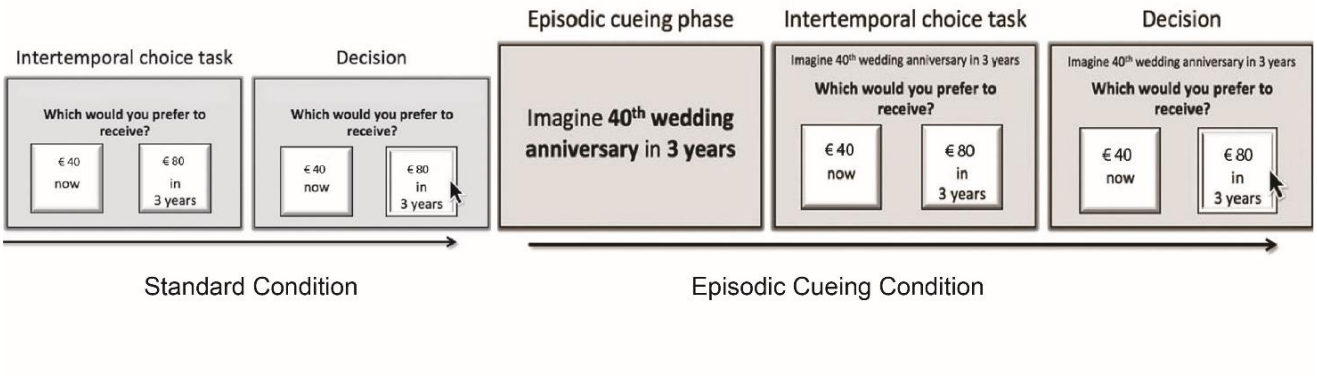
Participants completed a computerized intertemporal choice task used in previous studies (Kwan et al., 2012; Kwan, Craver, Green, Myerson, & Rosenbaum, 2013; Kwan et al., 2015) in two experimental conditions (see Figure 17). In the Standard condition, participants made a series of choices between two hypothetical monetary rewards - a smaller, immediate amount and a larger, future amount. For each of two future amounts of different magnitude (for the Italian sample: 80€ and 1500€; for the Canadian sample: $100 and $2000), participants made six choices for each of seven delays (1 week, 1 month, 3 months, 6 months, 1 year, 3 years, and 10 years), with delays presented in random order. The first choice at each delay was between the future amount and half that amount to be received immediately. For each of the subsequent choices at each delay, the amount of the immediate reward was adjusted based on the participant's previous choice. If the participant chose the immediate reward, then the amount of the immediate reward was decreased on the next trial; if the participant chose the delayed reward, then the amount of the immediate reward was increased on the next trial. After the first choice, the size of the adjustment to the immediate reward was half of the smaller amount. Subsequently, the size of the adjustment to the immediate reward decreased with each successive choice and was always equal to half of the previous adjustment, rounded to the nearest euro/dollar. This iterative procedure converged rapidly on an estimate of the amount of an immediate reward equivalent in (subjective) value to the delayed reward (see Green & Myerson, 2004 for further task details).

In the episodic cueing condition, participants first identified plausible personal future events (e.g., appointments, anniversaries, outings) for each of the seven delays in the discounting task. Participants were asked to include only emotionally neutral or positive future events. When participants encountered difficulties providing an event, the experimenter probed with the following questions: "Might there be any events with family or friends that may take place in <insert delay>?" and/or "Is there something you could possibly see yourself doing in <insert delay> or want to do in <insert delay>?". Participants were also allowed to refer to personal calendars and electronic

devices. The DD task then proceeded as in the standard condition, except that each delay-interval block was preceded by the prospective cue associated with that delay (Fig. 2). Thus, for each delay, participants were cued to imagine the personal event they had associated with that delay in as much detail as possible. They pressed a button indicating they had the event in mind, which triggered a screen prompting them to make a choice involving a reward at that delay. The event cue remained at the top of the screen until the end of the delay block to reduce demands on memory.

For all participants, the episodic cueing condition was run approximately one month after the standard condition. The experiment was blocked in this fashion to prevent any benefit from future event cueing from carrying over into participants' baseline discounting rates. Although carry-over effects from this design cannot be ruled out, they are unlikely: we have observed that repeated testing does not systematically change rates of discounting in amnesic cases or controls (Kwan et al., 2012; Kwan, Craver, Green, Myerson, & Rosenbaum, 2013; Kwan et al., 2015).

Figure 17. Experimental paradigm for the episodic cueing condition. Participants were presented with an episodic cue and imagined a personal future experience occurring at a specific delay (e.g., 3 years). They were then presented with two hypothetical rewards and indicated their decision between the smaller immediate reward and the larger reward to be received at the same delay.



Data analysis

The rate at which the subjective value of a reward decays with delay (DD rate) is generally assessed through two indices: the delay discounting parameter k (Rachlin, Raineri, & Cross, 1991; Green & Myerson, 2004), and the area under the empirical discounting curve (AUC) (Myerson, Green, & Warusawitharana, 2001). First, the hyperbolic function $SV = 1/(1 + kD)$, where SV is the subjective value (expressed as a fraction of the delayed amount), and D is the delay (in days), was

fit to the data to determine the *k* constant of the best fitting delay discounting function, using a nonlinear, least-squares algorithm (as implemented in Statistica; Statsoft). The larger the value of *k*, the steeper the discounting function, the more participants were inclined to choose small-immediate rewards over larger-delayed rewards. We then checked whether the exponential model proved equally able to capture DD behavior in patients and controls, and found this was not the case. The ANOVA on R^2 hyperbolic values with Group (vmPFC patients, healthy controls), Condition (standard, episodic cueing), and Reward magnitude (€80/$100, €1500/$2000) as factors, revealed a significant effect of Condition ($F_{1,52} = 8.84$, $p = 0.004$), and a significant Condition X Group interaction ($F_{1,52} = 5.13$, $p = 0.03$). Post-hoc Newman–Keuls comparisons showed that R^2 values were comparable in vmPFC patients and controls in the standard condition (0.71 vs. 0.62; $p = 0.35$), but they were significantly lower in patients than in controls in the episodic cueing condition (0.38 vs 0.58; $p = 0.04$). Furthermore, whereas controls had comparable R^2 values in the standard (0.62) and episodic cueing condition (0.58, $p = 0.62$), vmPFC patients reported significantly higher R^2 values in the standard than in the episodic cueing condition (0.71 vs 0.38, $p = 0.003$). No other effects were significant (all $p > 0.34$). Thus, in the episodic cueing condition, the hyperbolic model did not fit vmPFC patients' delay discounting function as it did for controls. Considering that DD behavior generally obeys a hyperbolic function in vmPFC patients, as shown by normal R^2 values in the Standard condition (see also Sellitto et al., 2010), we think that this finding reflects vmPFC patients' episodic future thinking impairment: vmPFC patients were inconsistently able to imagine future events across different delays, and therefore choices relative to some delays benefited disproportionately more than others from episodic cueing more, altering the shape of the DD function in a non systematic fashion. A corollary analysis showed indeed that although in the Standard condition vmPFC patients made a number of inconsistent choices (i.e., the subjective value of the future outcome at a given delay is greater than that at the preceding) comparable to the controls (see also Sellitto, Ciaramelli, & di Pellegrino, 2010), they made more inconsistent choices

than healthy controls in the episodic cueing condition, as expected if the success of episodic cueing fluctuated non systematically across delays (see Supplementary materials for more detail).

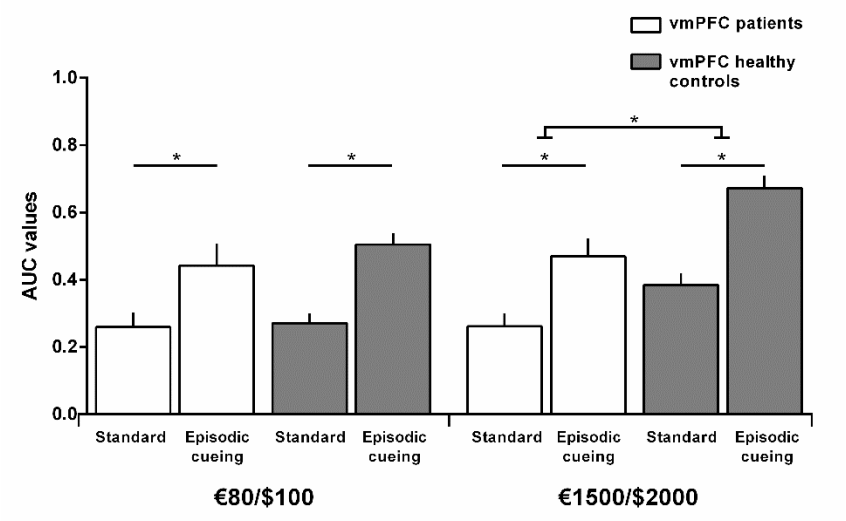
We elected the AUC as a measure of DD rate in our groups, as it is a normalized measure of the degree of reward discounting that is independent of any theoretical hypothesis concerning the precise shape of the discounting curve (AUC; Myerson, Green, & Warusawitharana, 2001). First, delays and subjective values were normalized. Each delay was expressed as a proportion of maximum delay (120 months) and subjective values were expressed as a proportion of the delayed values (€80/$100, €1500/$2000). The normalized delays were then plotted on the *x* axis and the normalized subjective values on the *y* axis as a function of delay to construct a discounting curve. Vertical lines were drawn from each *x* value to the curve, subdividing the area under the curve into a series of trapezoids. The area of each trapezoid was calculated as $(x2 - x1)(y1 + y2)/2$, where $x1$ and $x2$ are successive delays, and $y1$ and $y2$ are the subjective values associated with those delays (Myerson et al., 2001). The AUC is the sum of the areas of all the trapezoids. The AUC varies between 0 (maximally steep discounting) and 1 (no discounting). The smaller the AUC, the steeper the TD, and the more participants were inclined to choose small immediate rewards over larger delayed rewards.

Results

Figure 18 shows AUC values by participant group, condition, and reward magnitude. AUC scores were normally distributed (Kolmogorov-Smirnov $d < 0.20$, $p > 0.20$ in all cases), and therefore, comparisons were performed using parametric statistical tests. An ANOVA on AUC scores with Group, Condition, and Reward magnitude as factors revealed a main effect of Reward magnitude ($F_{(1,52)} = 14.78$, $p < 0.001$), a marginally significant effect of Group ($p = 0.06$), and a significant Group X Reward interaction ($F_{(1,52)} = 9.84$, $p = 0.003$). Newman-Keuls post hoc comparisons revealed that vmPFC patients had steeper DD than healthy controls for large rewards ($p = 0.01$) but not for small rewards ($p = 0.79$). Interestingly, healthy individuals discounted smaller

rewards more steeply than larger rewards ($p < 0.001$), replicating the magnitude effect (Thaler, 1981; Green, Myerson, & Mcfadden, 1997; Green, Myerson, & Ostaszewski, 1999), whereas vmPFC patients showed comparable delay discounting for both reward magnitudes ($p = 0.62$). Crucially, there was a significant main effect of Condition ($F_{(1,52)} = 62.23$, $p < 0.0001$), such that future rewards were discounted less steeply in the episodic cueing condition compared to the standard condition in both groups. No other effect or interaction was significant ($p > 0.26$ in all cases). To quantify directly the benefit from episodic cueing, we also calculated for each participant and reward magnitude the difference in AUC between the Standard and the Episodic cueing condition. The ANOVA on AUC difference scores with Group and Reward magnitude as factors revealed no significant effects ($p > 0.26$ in all cases), further confirming that vmPFC patients benefited from episodic cueing as much as controls.

Figure 18. Area under the empirical discounting curve by participant group (vmPFC patients, healthy controls), task condition (standard, episodic cueing) and reward (€80/$100 and €1500/$2000).



Discussion

This study investigated the effect of episodic future thinking (EFT) on intertemporal choices in a population of patients with damage to the ventromedial prefrontal cortex (vmPFC), a brain region known to play a necessary role in both EFT and the valuation of future rewards during intertemporal choices. To this aim, we tested vmPFC patients and matched healthy controls on a

delay discounting (DD) task, involving choices between smaller, immediate monetary rewards and larger, delayed rewards of two different magnitudes available at each of seven specified delays, both with and without episodic cueing. In the episodic cueing condition, participants were cued to imagine a personal event to occur at one of the delays immediately before a choice involving a reward at that delay. The main finding of the present study is that vmPFC patients had a reduced DD in the episodic cueing condition compared to the standard condition, showing a cueing effect similar to that observed in healthy controls. Furthermore, vmPFC patients had steeper DD than healthy controls only for large rewards, related to the fact that they discounted small and large reward magnitudes to the same extent, thus not showing the same magnitude effect observed in healthy controls, who discounted larger rewards less steeply than smaller rewards.

The finding that vmPFC patients reduce their tendency to discount future rewards when they are cued to imagine personal future events is intriguing, considering that neuroimaging findings in healthy individuals show that the episodic future thought reduces delay discounting via activation of the vmPFC (Benoit, Gilbert, & Burgess, 2011), and that the strength of episodic cueing effect is associated with increased functional coupling between the hippocampus and medial prefrontal regions (Peters & Büchel, 2010), areas typically associated with reward processing (McClure et al., 2004; Kable & Glimcher, 2007) and future thinking (Addis, Wong, & Schacter, 2007; Botzung, Denkova, & Manning, 2008). However, the presence of an episodic cueing effect in vmPFC patients is consistent with a similar reduction of delay discounting through episodic future thinking found in people suffering from different forms of addiction, like alcohol (Snider, LaConte, & Bickel, 2016), food (Daniel et al., 2013; O'Neill, Daniel, & Epstein, 2016) or drugs (Dennhardt et al., 2015; Stein et al., 2016) abuse, and in young healthy people, like adolescents (Bromberg, Lobatcheva, & Peters, 2017). Interestingly, individuals in such clinical conditions as well as those in the early stage of life share with frontal patients many cognitive and behavioral features. The first feature they have in common is a poor decision-making and impulse control ability. Indeed, individuals with alcohol dependence (Petry, 2001), affected by obesity (Weller, Cook III, Avsar, &

Cox, 2008; Davis, Patte, Curtis, & Reid, 2010) or drugs addiction (Madden, Petry, Badger, & Bickel, 1997; Kirby, Petry, & Bickel, 1999; Coffey, Gudleski, Saladin, & Brady, 2003), and adolescents (Olson, Hooper, Collins, & Luciana, 2007; De Water, Cillessen, & Scheres, 2014), show an inability to delay gratification, indexed by steeper discount rates compared to healthy/older individuals. The second feature that addicts, young healthy people and vmPFC patients have in common is poor long-term memory and future thinking abilities. Individuals with alcohol dependence or drugs abuse show difficulties in the recollection of personal past episodes (Rogers & Robbins, 2001; Verdejo-Garcia, Lopez-Torrecillas, Orozco Gimenez, & Perez-Garcia, 2004; D'Argembeau, Van der Linden, Verbanck, & Noe, 2006; Pitel et al., 2007; Solowij et al., 2011; Noël et al., 2012; Schuster, Crane, Mermelstein, & Gonzalez, 2015; Nandrino et al., 2016), and in the imagination of novel future scenarios (Griffiths et al., 2012; Mercuri et al., 2014; Mercuri et al., 2016). A similar change in episodic memory and future thinking occurs across life span, with younger children telling less coherent and less rich events than older children, irrespective of temporal direction (Bohn & Berntsen, 2013; Gott & Lah, 2013).

An effect of episodic future thinking on delay discounting seems to be surprising in clinical populations with difficulties in imagining the future. Studies on people with different forms of substances abuse (Daniel et al., 2013; Snider et al., 2016; Stein et al., 2016) or on adolescents (Bromberg et al., 2017) have attributed the reduction of future rewards discounting to a shifting in time perspective and a widening of individual's temporal window induced by episodic future thinking, resulting in an easier valuation of future consequences, that leads to increased self-control and likelihood of acting in one's long-term best interest (Bickel, Quisenberry, Moody, & Wilson, 2015; Snider et al., 2016; Stein et al., 2016). However, the strength of the episodic effect in healthy individuals is usually associated with the vividness of the imagined future events (Peters & Büchel, 2010), whereas studies on alcohol addicts (Snider et al., 2016) and adolescents (Bromberg, Lobatcheva, & Peters, 2017) did not find such an association, leading to wonder which quality of the future scenarios triggered the effect and to question the actual participants' engagement in the

simulation of future events in an episodic way. Although we did not measure the vividness of the imagined future episodes in the current study, a similar doubt arises for the strategy used by vmPFC patients during the episodic cueing condition. These patients are indeed known to be impaired at constructing and visualizing future events (Bertossi, Aleo, et al., 2016; Bertossi, Tesini, et al., 2016; Bertossi, Candela, De Luca, & Ciaramelli, 2017).

To explain which type of strategy vmPFC patients used during the episodic condition of the task, it may be useful to call into question their spared cognitive abilities. Semantic memory is one of them. Indeed, vmPFC patients can provide a number of external (non episodic) details, which include semantic information, comparable to that of healthy controls (Bertossi, Tesini, et al., 2016; Bertossi, Candela, De Luca, & Ciaramelli, 2017), when asked to recall past episodes or imagine future events. Similarly, vmPFC patients are capable to make judgements about the semantic content of single scenes to detect semantic impossibilities (e.g., an elephant with butterflies for ears; De Luca et al., under revision). Thus, one possibility is that vmPFC patients exploited their spared personal semantic knowledge (Tanguay et al., 2018) as a less demanding, shortcut-strategy to supply an impaired episodic future thinking, and that their 'semanticized' anticipation of the future was enough to improve delay discounting. On this account, semantic memory would be sufficient to engage in a collateral form of future simulation and, consequently, to modify own' choices accordingly. If this was the case, however, amnesic patients with MTLs damage should benefit from episodic cueing to the same extent than vmPFC patients.

Another possibility is that episodic cueing in vmPFC (but not in MTLs) patients had an effect on DD because, as my previous experiments 3 and 4 suggest, vmPFC patients are particularly impaired during unconstrained tasks, like simulation of past, future or fictitious scenarios (Bertossi, Aleo, et al., 2016; Bertossi, Tesini, et al., 2016; Bertossi et al., 2017), because they find it difficult to initiate endogenous processing related to access, filter and collect the contents of cognition. However, when such processing is circumvented with the provision of structured cueing to concrete future events, like in the current task, then a deficit may be no longer apparent, consistent with

evidence of an effect of EFT on delay discounting (McCormick et al., 2018; De Luca et al., under revision). On the other hand, the finding that patients with the most widespread and bilateral damage within the MTL (including the hippocampus) were the least responsive to the episodic cueing (Kwan et al., 2015; Palombo, Keane, & Verfaellie, 2015) leads to think that MTL structures play a role during the construction of episodic future scenarios that cannot be circumvented by providing a scaffold for future imagining. Thus, vmPFC patients are impaired at self-initiating the event construction process, but if they are provided with structured cueing, which acts as an external construction "inducer", they become able to simulate future scenarios, and to factor them into intertemporal choice, whereas MTLs patients are unable to mentally construct specific events no matter how much construction was externally prompted, and therefore cannot benefit from EFT during decision making. This interpretation is in line with the proposal that vmPFC and the hippocampus may work in concert during the construction of scenes, playing different complementary roles (McCormick, Ciaramelli, et al., 2018).

This study also replicates the finding of an increased devaluation of future rewards during intertemporal choices after vmPFC damage (Sellitto et al., 2010), but it adds new information about the valuation of the magnitude of future rewards to be discounted. Indeed, vmPFC patients had a steeper DD than healthy controls only for large rewards, related to the fact that, unlike healthy controls, they discounted in a similar way rewards of different magnitudes. The lack of a magnitude effect (Thaler, 1981; Green et al., 1997; Chapman & Winquist, 1998; Green, Myerson, & Ostaszewski, 1999) in vmPFC patients is in line with extant studies in animals (van Duuren, Lankelma, & Pennartz, 2008; da Costa Araújo et al., 2010; Ostrander et al., 2011) and humans (Knutson, Taylor, Kaufman, Peterson, & Glover, 2005; Ballard & Knutson, 2009), showing that medial prefrontal cortex and nucleus accumbens are associated with the valuation of the size of future rewards. fMRI studies in humans found that activation in medial prefrontal cortex correlates with increasing magnitudes of future rewards and, of note, more impulsive individuals show diminished neural activation to larger future rewards (Ballard & Knutson, 2009).

Indeed, prefrontal areas necessary for executive control are more strongly engaged in choices involving high-magnitude options (Ballard et al., 2017), which have been deemed to entail higher levels of self-control. Self-control is considered a determinant factor of the magnitude effect in intertemporal choice: being self-control effortful, it is flexibly allocated according to the perceived importance of the decision (McGuire & Botvinick, 2010; Shenhav, Botvinick, & Cohen, 2013). It is reasonable to think that larger rewards are deemed to deserve more effort than smaller rewards. As mentioned above, self-control is associated to the activity of the frontal lobes (Menon, Adleman, White, Glover, & Reiss, 2001; Garavan, Ross, Murphy, Roche, & Stein, 2002; Aron, Robbins, & Poldrack, 2004; Aron, Robbins, & Poldrack, 2014) and vmPFC patients have poor decision-making and self/impulse control (Clark, Cools, & Robbins, 2004; Bechara, 2004; Cato, Delis, Abildskov, & Bigler, 2004; see Bechara & Van Der Linden, 2005 for a review). Therefore, it is possible that poor self-control led vmPFC patients not only to discount inconveniently larger future rewards more steeply than the smaller immediate ones, but also to neglect the advantage of choosing future rewards of larger magnitude.

The lack of magnitude effect in vmPFC patients seems to be successfully explained by the self-control hypothesis, but it could be also accounted for by the discounted utility model of rational choices, which posits that individuals assess rewards with a utility function that has increasing proportional sensitivity (Prelec & Loewenstein, 1991; Loewenstein & Prelec, 1992). According to this model, the magnitude effect is believed to be an anomaly of decision-making process, because it leads individuals to assume that the ratio between the utilities of $20 and $10 is smaller than the ratio between the utilities of $2,000 and $1,000, and so that the larger reward in the high-magnitude condition is relatively more valuable than the larger reward in the low-magnitude condition (Loewenstein & Prelec, 1992). As an irrational form of thought occurring during economic choices, the magnitude effect is comparable to other anomalies of the decision-making process involving time delay or uncertainty, like the “certainty effect” (Kahneman & Tversky, 1979) or the “Allais paradox” (Allais, 1953), the tendency to overweight outcomes that are certain relative to those that

are probable, even when the certain are less convenient. These effects have been explained as a mechanism to anticipate and avoid the feeling of regret associated to the acknowledgment of having lost a more desirable option than the chosen one (Loomes & Sugden, 1982; Bourgeois-Gironde, 2010). It is possible that the tendency to discount less steeply larger than smaller rewards follows the similar need to avoid the regret that would arise if a smaller, less advantageous future reward had chosen over a larger, more advantageous one. If it is the case, an inability to experience regret would prevent to show the magnitude effect. The orbitofrontal cortex has been found to represent the impact of potentially negative consequences of choices during the comparison between actual outcomes and counterfactual ones (Ursu & Carter, 2005) and vmPFC patients are, indeed, incapable to modify their behavior in response to negative consequences (Rolls, 2000) and to take regret into account during decision-making (Camille et al., 2004). Therefore, it is possible that vmPFC patients, not being able to pre-experience the future disappointment associated with a less convenient choice, fail to appreciate the difference between the two reward magnitudes, ending up discounting the two magnitudes in a comparable way.

To conclude, we have showed that vmPFC patients had steeper DD than healthy controls, though this was mainly apparent with large future rewards. Crucially, cueing personal future events proved normally effective in decreasing discounting of future rewards in vmPFC participants as well as healthy controls, reducing the difference in DD behavior between groups. This finding shows that, although vmPFC patients' future thinking is poor in episodic detail, it may be sufficient to modulate the value assigned to future rewards, perhaps by externally activating personal semantic structures necessary for future-oriented decision making.

CONCLUSION

The present thesis has addressed the cognitive and neural mechanisms underlying the complex act of constructing mental events. I have mainly focussed on one specific form of mental event construction, episodic future thinking. The important cognitive and neural similarities between episodic future thinking and remembering the past have raised several hypotheses about the core component processes shared by these abilities. One account has emphasized the constructive nature of both abilities, suggesting that elements of episodic memory are extracted and flexibly recombined to construct novel events; another account has instead focussed on the common process of self-projection into alternative situations that episodic memory and episodic future thinking share with other forms of mental simulations, as theory of mind and spatial navigation; in contrast with this last approach, it has been suggested that scene construction, i.e., the generation, visualization and maintenance of mental scenes, is the fundamental process underlying the construction of any mental event, not only future, but also past, atemporal experiences, and even experiences not related to the self.

The first chapter of the present thesis has addressed the nature of the cognitive relationship between episodic memory, episodic future thinking and future-based decision making and cognition, through a single case of retrograde amnesia, which causes a severe impairment of episodic – autobiographical memory, leaving partially spared the semantic memory component. Study 1 showed that episodic – autobiographical memory is necessary to envision personal future events, but not to construct fictitious, atemporal experiences, to make future-oriented decisions, or to conceive the concept of time, and that semantic memory can be sufficient for some forms of mental event construction. The second chapter of the thesis has begun to explore the neural bases of the mental construction of future events, investigating component processes of episodic future thinking and the role of vmPFC in this ability, through the study of patients with damage to the vmPFC. Study 2 confirmed that vmPFC is necessary for the construction of personal future events, and showed that vmPFC is also involved in narrative and working memory abilities. Importantly,

however, poor narrative and working memory abilities have not been found to explain the episodic future thinking impairment that follows a vmPFC damage.

The third chapter has deepened the investigation of the role of vmPFC in event construction, narrowing the focus on a core component process of event construction, namely, the construction of scenes, and on the role of vmPFC and hippocampus in this process. vmPFC and hippocampus are key nodes of the construction system and both necessary to construct mental scenes; thereby, this chapter has tried to differentiate their distinct contribution to the scene construction process. Study 3 has addressed explicit and implicit scene construction processes, whereas study 4 has probed the constructive and semantic components of the scene construction process. Findings showed that vmPFC and hippocampus are both necessary for explicit and implicit scene construction processes; however, the different profile of impairment of vmPFC and hippocampal patients led us to suggest that vmPFC is critical to initiate endogenous processes related to the construction of content-rich scenes, whereas the hippocampus is specifically involved in assembling scenes in a coherent spatial context.

The last chapter comes back to examining one specific form of mental event construction, episodic future thinking, focusing on its effect on decision making, in patients with damage to the vmPFC. Study 5 showed that although vmPFC patients have impaired episodic simulation and delay discounting behavior, they show reduced delay discounting when cued to imagine the future before making intertemporal choices. We have argued that vmPFC patients' main problem is at self-initiating event construction, and that providing structured cues to construct a (albeit semanticized) representation of the future improves future-oriented choice in these patients. This study, therefore, confirmed that vmPFC is involved in the self-initiation of the mental event construction, and that decision-making abilities can benefit from the externally induced simulation of future events.

To conclude, the present thesis has discussed the cognitive and neural mechanisms underlying the complex act of constructing mental events, focussing on the core process of scene construction and on the different roles played by vmPFC and the hippocampus in this process. The

reported findings provide further support to the scene construction theory, by showing the necessary roles played by vmPFC and hippocampus during the construction of mental scenes, and proposing a hierarchical model of their interaction during scene/event construction. Scenes are the backbones of any simulated extended event, necessary to construct past, future and atemporal experiences and involved in some aspects of decision making. The construction of mental events is a vital feature of human mental activity, allowing individuals to engage in high-order forms of cognition, as remembering personal past, imagining personal future, or mind-wandering, abilities highly related to self-identity and self-consciousness, and that are claimed to distinguish humans from other species. Therefore, it seems of particular interest to understand how and where in the brain such complex experiences are constructed and used. Further research is needed to continue the investigation of the component processes and the neural underpinnings of such a complex human mental faculty.

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