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THE ROLE OF VENTROMEDIAL PREFRONTAL CORTEX IN MENTAL TIME TRAVEL AND MIND WANDERING

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Abstract

Recent research has contributed to characterize a network of brain regions known as the Default Mode Network (DMN), including the ventromedial prefrontal cortex (vmPFC), which is active when individuals remember the past, imagine the future, take the perspective of others, as well as during mental navigation and spontaneous cognition (mind wandering). It is not clear, however, which is the specific role of different nodes of the DMN during mental time travel (MTT) and mind wandering. The overarching goal of this dissertation is to investigate whether the vmPFC plays a crucial role during DMN-related cognitive processes, such as episodic memory, future thinking, and mind wandering. Experiment 1 revealed that a damage to the vmPFC provokes the disruption of past and future MTT and a decreased ability to imagine future other-related episodes. These findings suggest a causal role of vmPFC in remembering the past and imagining the future. Its role extends to imagining events that are not self-relevant indicating that vmPFC is crucial for the imagination of complex experiences alternative to the current reality, which serves construction of both self-relevant and other-relevant events. This hypothesis was confirmed in experiment 2. Findings showed that a lesion to vmPFC disrupts also the ability to construct complex atemporal scenarios. However, unlike the control groups, vmPFC patients had more difficulties in imagining future compared to fictitious experiences, suggesting that vmPFC is even more critical for the simulation of personal future episodes, when a sense of subjective time is involved. In experiment 3, the involvement of vmPFC in simulating future experiences was confirmed and it revealed that these results are not explained by the disruption of non-episodic capabilities, such as narrative and working memory abilities. Furthermore, experiment 4 explored the

effect of a lesion to vmPFC on the occurrence of mind wandering. A damage to the vmPFC provokes a decreased propensity to mind-wander, showing that vmPFC supports spontaneous thoughts that allow a shift of attention from the current activity toward internal mentation. Experiment 5 confirmed the involvement of the medial prefrontal cortex (mPFC) in supporting mind wandering. Using the transcranial direct current stimulation (tDCS) to inhibit the mPFC we could decrease the intensity of mind wandering in males. Together, these results point out the fundamental role of vmPFC in allowing human beings to escape the here and now, whether it occurs deliberately or spontaneously.

1 General introduction

The frontal lobes occupy almost one third of the cortical area of the brain in humans (Mesulam, 2002). The cortex of the anterior part of the mammalian brain is commonly called the prefrontal cortex. The prefrontal cortex enlarged in size with phylogenetic development and reached the maximal development in humans. The greater size of the human prefrontal cortex may indicate that this cortex is the substrate for cognitive functions of the highest order (Fuster, 2008). The prefrontal cortex is a collection of neocortical areas that interact through projections with subcortical areas, sensory, and motor systems (Miller and Cohen, 2001). Different areas within the prefrontal cortex may have different functions. Two main networks are present in the prefrontal cortex: a dorsolateral parietal system that is related to working memory and related cognitive functions, and a ventromedial system that is linked to memory, motivation, visceral functions, and emotions (Mesulam, 2002).

Of special interest in this thesis is the ventral part of the medial prefrontal cortex (vmPFC). The vmPFC is centered along the inferior portion of the medial wall of the frontal lobe, however, the precise borders of the vmPFC are not always well-defined (Zald and Andreotti, 2010). Öngür and Price (2000) defined two networks within the human orbital and medial prefrontal cortex: the orbitofrontal network that includes Broadmann Areas (BAs) 12 and 13, and the medial frontal network that comprises the BAs 9, 10, 11, 24, 25, and 32 (Ongür and Price, 2000; Nieuwenhuis and Takashima, 2011). Most of vmPFC, which is the area of interest in this dissertation, is included in the medial frontal network. In some cases a damage to vmPFC can be caused by the rupture of an aneurism in the anterior communicating artery (ACoA), located at the circle of Willis at the ventral portion of the brain. Possible consequences of lesions to the vmPFC are memory deficit, confabulation, and changes in personality (DeLuca and Diamond, 1995). The ventral frontal damage can also provoke deficits in behavioral control (Bechara et al., 1994) and decision making (Fellows and Farah, 2007).

The vmPFC is part of a network of brain regions, called the Default Mode Network (DMN), that is particularly active when individuals remember past events, imagine future events, and, in general, simulate experiences alternative to the present in a spontaneous or deliberate manner (Shulman et al., 1997; Gusnard and Raichle, 2001; Mazoyer et al., 2001; Hassabis et al., 2007a; Buckner et al., 2008; Christoff et al., 2009; Spreng and Grady, 2010). Based on these studies (see also chapters 2, 3, and 4), it is possible to hypothesize that the vmPFC is critical for supporting the ability to travel mentally in time, i.e., remember past events and imagine future events, and to mind-wander, i.e., shifting one's attention to mental contents unrelated to the current activity. In the current dissertation we aimed to answer different experimental questions about the role of vmPFC in MTT and mind wandering using a lesion approach. Is vmPFC crucially involved in MTT, and, if so, is vmPFC equally important for supporting the capability to remember the past and to imagine the future? Is vmPFC critical for projecting oneself in time and for imagining other-related experiences? Does vmPFC support the construction of complex atemporal experiences? Is it possible that non-episodic abilities mediated by vmPFC, such as narrative and working memory abilities, affect episodic construction in patients with vmPFC damage? Finally, is vmPFC critical for allowing individuals to escape from the here and now in a spontaneous manner, as it occurs while individuals mind-wander during a task?

In the next three chapters, I will delineate the theoretical concepts and the studies on the neural bases of MTT and mind wandering (see chapters 2, 3, and 4). Next, five experiments will be described through which we aimed to answer the aforementioned experimental questions.

In experiment 1 (chapter 5), I studied how vmPFC patients and healthy controls remember personal past events and imagine personal future events at different timeframes, and how they imagine events that may happen to a “close” other (family member) or a “distant” other (President of the Italian Republic). Compared to the healthy controls, vmPFC patients were impaired at constructing both past and future events, indicating that vmPFC is critical for MTT. Patients, however, were also impaired at imagining other-related events, suggesting that self-relevance may not be a critical factor in explaining vmPFC’s involvement in allowing individuals to mentally escape from the here and now.

In experiment 2 (chapter 6), to test whether vmPFC is crucial for episodic future thinking (EFT), or it is critical for supporting the construction of any kind of atemporal complex experiences, I studied how patients with focal lesion to vmPFC, control patients with lesions outside the vmPFC (mainly occipital), and healthy individuals imagine future and fictitious experiences. Compared to the control groups, vmPFC patients were impaired at imagining both future and fictitious experiences, indicating a general deficit in constructing novel experiences. Unlike the control groups, however, vmPFC patients had more difficulties in imagining the future compared to fictitious experiences.

In experiment 3 (chapter 7), I explored the possibility that differences in imagining the future between vmPFC patients and healthy controls are due to non-episodic abilities such as the capability to verbally describe a complex scenario and maintain it in working memory. To test these hypotheses, we asked vmPFC patients and healthy participants to imagine future episodes using pictures as cues or to perform a picture description task in two conditions: in the presence of a picture (description condition) or in absence of a picture after an observation phase (working memory condition). Results show that poor performance in imagining the future in vmPFC patients is not fully explained by a deficient capability to describe complex images or to maintain them in working memory. Indeed, group differences in imagining the future remain also when we controlled for these variables.

In experiment 4 (chapter 8), mind wandering and its phenomenology have been examined in vmPFC patients, control patients with lesions not involving the vmPFC, and healthy individuals. Participants performed three tasks varying in cognitive demands (Smallwood et al., 2009). While doing the tasks, they were asked to report the degree to which their thoughts were on-task or off-task and classify the contents of their off-task thoughts. vmPFC patients engaged in mind wandering less frequently than both control groups, whereas no significant difference was found between the two control groups. Importantly, the content of mind wandering experienced by vmPFC patients was never future-related. These findings suggest that vmPFC is a fundamental hub of a set of brain regions that supports mind wandering.

In experiment 5 (chapter 9), the role of the medial prefrontal cortex (mPFC) in sustaining spontaneous cognition was investigated using transcranial direct current stimulation. An activation likelihood estimation (ALE) meta-analysis was conducted for investigating which brain areas are associated with mind wandering experiences. Next, in order to check the specificity of medial prefrontal involvement in spontaneous cognition, mind wandering experiences were collected before and after the administration of transcranial direct current stimulation on mPFC (brain area location was chosen upon the ALE meta-analysis results) (mPFC-tDCS), and on a control medial occipital cortex region (OC-tDCS). A sham group was also included. We found that cathodal stimulation on the mPFC reduced the intensity of mind wandering. This effect was not present for OC-tDCS and sham groups and emerged specifically in male participants.

Finally, after the description of the aforementioned experiments, a general discussion will follow (chapter 10).

2 Mental time travel

2.1 Remembering the past and imagining the future: theoretical concepts

Mental time travel (MTT) is a term conceived by Suddendorf and Corballis (1997) and it refers to the capability to mentally (re-)create experiences staged in the past or in the future. This phenomenon is called MTT because is similar to a mental journey that covers specific past episodes or specific future experiences. Travelling mentally backwards in time means to recall episodic memories that derive from events personally experienced (Tulving, 1983, 1985). Episodic memory refers to individuals' ability to retrieve past events from one’s life, it is about happenings personally experienced in particular places at particular times, about the “what”, “where”, and “when” they occurred (Tulving, 1985, 2001). Episodic memory is often defined in contrast to semantic memory which is the memory for general knowledge of the world, such as concepts, vocabulary, and facts, no longer tied to the context of acquisition (Tulving, 1972, 1985). Remembering the past and communicating past episodes to other individuals is advantageous for human beings. It permits to exchange fundamental information, avoid making again previous mistakes, make effective decisions, and maintain social relationships (Alea and Bluck, 2003; Suddendorf and Corballis, 2007).

Episodic future thinking (EFT) is the capability to mentally travel into the future and envisioning oneself participating in future experiences. EFT is a pervasive phenomenon in daily life and often it involves inner speech and mental imagery (D'Argembeau and Mathy, 2011; Demblon and D'Argembeau, 2014). Imagining the future allows individuals to reach their goals, cope with future problems, regulate emotions, and make adaptive decisions (Atance and O'Neill, 2001; Quoidbach et al., 2009; Szpunar, 2010).

There are some capacities that may be necessary to engage in MTT (Suddendorf and Corballis, 2007). It is critical to create a mental "space" that permits a combination of different pieces of information. A possible candidate ability for supporting the combination of different pieces of information is working memory, which allows maintenance and manipulation of information, such as episodic, perceptual, and emotional details. The elements (details) that are recombined together for simulating future events likely come from declarative memory (Schacter and Addis, 2007). The main characters of the events during a temporal mental journey can be oneself and/or other individuals. In order to simulate others' actions it is essential to have knowledge about their beliefs, goals, and desires. This level of knowledge permits to understand that individuals' mental states are not rigid and can change in the past, present, and future. In order to imagine future scenarios the ability to evaluate different alternatives and judge their desirability and likelihood is needed. Finally, simulations of past and future events are often communicated using language and narrative abilities. The communication to others of past and future events has important social functions, for instance maintaining relationships, teaching, informing others, and arising empathy (Alea and Bluck, 2003).

Another property that characterizes the ability to travel mentally in time is autonoetic consciousness (self-knowing consciousness), that is the understanding of the extended existence of the self in the past, present, and future (Tulving, 1985; Wheeler et al., 1997). Tulving distinguished autonoetic consciousness from noetic consciousness which refers to the awareness of existence of the world, objects, events, and their regularities, and from anoetic consciousness that describes the simple awareness of external stimuli that does not allow to escape mentally from the here and now (Tulving, 1985, 2001). Autonoetic consciousness was hypothesized to be supported by the frontal lobes (Wheeler et al., 1997).

A possible link between episodic memory and EFT derives from the idea that remembering an episode is a constructive process and not a mere repetition of the past (Bartlett, 1932). Indeed, memory does not store perfect replicas of experiences but it is a constructive process in which pieces of information from different sources are assembled together. A critical evidence that memory is a constructive process come from the observation of typical memory errors and distortions that result from mistakenly combining pieces of information, for example, remembering to have purchased something that you did not. It is common to make such mistakes while remembering past episodes, and precisely the constructive and flexible nature of memory comes at the cost of vulnerability to distortions and errors (Schacter et al., 2011; Schacter, 2013). Because the constructive nature of episodic memory makes it highly flexible and adaptive, it was hypothesized that the function of the constructive aspects of episodic memory is to allow individuals to simulate events that might occur in the future (Schacter and Addis, 2007). Indeed, Schacter and Addis (2007) proposed that construction of future events relies on recombining elements of past episodes, which draws on relational processes (constructive episodic simulation hypothesis). Evidence for the constructive episodic simulation hypothesis comes from a study by Addis and colleagues (2009a). Using a recombination paradigm in which details from participants' personal past experiences were recombined for imagining past and future events, authors found evidence of a common network active during remembering and imagining events in prefrontal regions, temporal lobe and parietal areas. These results suggest a common nature of remembering and imagining the future, which reflect the flexible nature of memory and the possibility that episodic past elements are employed to construct future episodes.

A concept that incorporates MTT but extends it to encompass other forms of simulations is self-projection (Buckner and Carroll, 2007). Self-projection is defined as the capacity to shift perspective from the immediate environment to alternative scenarios, such as remembering the past and imagining the future, but also conceiving the viewpoint of others and mental navigation. Buckner and Carroll (2007) hypothesized that there is a brain network of fronto-temporal-parietal areas that enables self-projection. Authors observed that this network is very similar to the DMN that is a set of brain regions that includes the mPFC, the posterior cingulate cortex/restrosplenial cortex, the medial and lateral temporal lobes, and the posterior inferior parietal lobes, active during relatively passive task and states, such as observing a fixation cross on a computer screen (e.g, Raichle et al., 2001). The similarity between self-projection network and the DMN raises the possibility that default mode of cognition that occurs, for example, during passive states, is characterized by a shift from perceiving the external environment to internal modes of cognition, that involve, for instance, simulating future experiences and remembering past episodes (Buckner and Carroll, 2007). Buckner and Carroll (2007), similarly to Schacter and Addis (2007) with their constructive episodic simulation hypothesis, hypothesized that self-projection depends on memory systems because past experiences represent the ground on which alternative experiences are created. The self-projection hypothesis and the constructive episodic simulation hypothesis share assumptions regarding the use of episodic information to simulate mental experiences. However, the self-projection hypothesis focuses on explaining the common ability to project the self in other times or other places, for instance when there is a transposition of the reference point, from here to there, from now to then, and from the self to others (Buckner and Carroll, 2007). On the other hand, the constructive episodic hypothesis focuses more on describing and explaining the process of constructive recombination of elements from memory necessary for constructing future experiences.

Hassabis and Maguire (2007) proposed another process, named scene construction, that may account for the similarities in the brain networks activated by different cognitive functions, such as MTT, navigation, and taking the perspectives of others. Scene construction is defined as a process that generates, visualizes, and maintains coherent scenes in the mind's eye. It was hypothesized that in order to imagine the future it is necessary to transfer the self in time (Atance and O'Neill, 2001). However, Hassabis and Maguire (2007) argued that individuals also imagine novel fictitious scenarios that are not temporal or self-relevant, for example imagining a white sandy beach in a beautiful tropical bay, and showed that this ability, too, relies on the similar brain network hypothesized to be active during MTT. Therefore, Hassabis and

Maguire pointed out that rather than self-projection, the process of scene construction is better able to account for similarities in brain activation during MTT, theory of mind, mental navigation, and default mode of cognition (Hassabis and Maguire, 2007). They hypothesized a crucial role of hippocampus in scene construction because it allows to process spatial information and bind together elements for constructing an imagined complex scenes. In support to the scene construction hypothesis, Hassabis and colleagues showed that remembering imagined or real memories and imagining new atemporal experiences recruited a common brain network including the medial temporal lobes (MTLs), posterior parietal cortices, and vmPFC (Hassabis et al., 2007a), those brain areas are also hypothesized to be involved in self-projection (Buckner and Carroll, 2007).

Here, the possible processes that underlie remembering autobiographical events and imagining future experiences were considered: autonoetic consciousness, episodic simulation, self-projection, and scene construction. All of them have been proposed to account for the similar neural bases of remembering the past and imagining the future. In the next two paragraphs, the neural bases of remembering the past and imagining the future are delineated, reporting evidence from neuroimaging and clinical studies in humans.

2.2 Neural bases of remembering the past and imagining the future: neuroimaging studies

Similar processes were hypothesized to underlie the abilities of remembering the past and imagining the future (Buckner and Carroll, 2007; Hassabis and Maguire, 2007; Schacter and Addis, 2007). Commonalities in the neural activity between EFT and episodic memory were observed across different neuroimaging studies (Okuda et al., 2003; Addis et al., 2007, 2009a; Szpunar et al., 2007; Botzung et al., 2008; Spreng et al., 2009; Spreng and Grady, 2010; Viard et al., 2011). In the previous paragraph we have delineated processes possibly underlying those commonalities. MTT and autonoetic consciousness focus on the importance of the temporal factors in explaining the similarities between remembering the past and imagining the future. Indeed, remembering past events and imagining the future have common neural bases because both activities involve the capacity to project oneself in time. However, other kind of mental simulations may have features in common with imagining future experiences, even though time is not involved, for example when individuals imagine to be in a different place (Schacter et al., 2012). Self-projection and scene construction can account also for these other forms of mental simulation, such as mental navigation, the construction of fictitious experiences, and taking the perspective of others, that are not related to temporal factors.

An evidence in favor of the autonoetic consciousness and MTT processes, comes from a study by Nyberg and colleagues (2010). In that neuroimaging study participants were required to remember a recent walk or imagine a future, present, or past walk along the same path. Brain activity during remembering a walk, and imagining past and future walks were compared with brain activity while participants were asked to take a mental walk along the same route in the present. Nyberg et al. (2010) showed that the parietal cortex, middle frontal gyrus, cerebellum, and thalamus were commonly engaged while participants remember and simulate the walks in the past or future compared to taking the same walk in the present. These results support the hypothesis that some brain regions are involved in MTT, thus, specifically when the temporal factor is considered. In another study (Arzy et al., 2008) participants were asked to change their self-location in time to the past, the now, or the future, and then to determine whether events happened before or will happen after the imagined self-location in time. Three brain regions were found to be recruited for self-location in time: the occipitotemporal cortex, the temporoparietal junction, and the anteromedial temporal cortex. Similar results were found in a related study by Arzy and colleagues (2009). Moreover, Szpunar et al. (2007) asked participants to remember past events and imagine specific future events, or imagine events involving a familiar individual. There was an overlap in activity associated with specific past and future events in the frontopolar and MTL regions, and posterior cingulate cortex. However, these regions were not active when imagining a familiar individual, suggesting that those brain areas are specifically critical for constructing personal experiences staged in time. Together these studies demonstrate that a set of brain regions is active specifically when individuals travel mentally in time, favoring the importance of temporal processes in explaining why common brain regions support the ability to escape from the here and now.

On the other hand, there are proofs about the existence of an atemporal perspective that may explain common brain activation while remembering the past and imagining the future (Schacter et al., 2012). Thus, the same common set of brain regions that are active during MTT could maintain any kind of mental simulation, also atemporal in nature. For instance, in a study by Spreng and colleagues (Spreng et al., 2009) the correspondence of neural activations across neuroimaging studies for autobiographical memory, EFT, mental navigation, and theory of mind was assessed using ALE meta-analyses. The authors analyzed the statistically significant concordance of activated voxels across neuroimaging experiments for each domain. Then, a conjunction analysis was employed to assess correspondence across domains by identifying whether clusters from different studies on different kinds of mental simulation converge across brain structures. The results provide evidence supporting the existence of a core set of brain regions within the DMN (see paragraph 2.1 and chapter 4) that underlie remembering, EFT, navigation, and theory of mind, suggesting the idea that common brain activation found during MTT may also be found for other kind of mental simulations that do not necessarily involve travelling mentally in time. In a study mentioned in the previous paragraph, Addis and colleagues (Addis et al., 2009a) found a functional network, similar to the DMN (see paragraph 2.1 and chapter 4), that included aspects of mPFC, inferior frontal gyrus, MTL, polar and posterior temporal cortex, medial parietal cortex and cerebellum, commonly engaged in simulating events that might have happened in the past and future experiences, suggesting once again that any kind of mental simulation is capable to activate brain regions within the DMN. Considering a different atemporal perspective, a possible explanation of the common brain activity during remembering the past and imagining the future could be that both capacities rely on scene construction (see paragraph 2.1). In a study we mentioned in the previous paragraph, participants were asked to recall recent episodic memories, retrieve fictitious experiences previously constructed, and imagine new atemporal experiences.

Common activations were found in the hippocampus, parahippocampal gyrus, retrosplenial cortex, and posterior parietal cortex, the middle temporal cortices, as well as the vmPFC. These results suggest that brain regions that are active during remembering real events are also engaged in imagining other kind of complex experiences (e.g., fictitious). This evidence supports the idea about the close relation between memory and imagination, irrespectively of the temporal factor.

As mentioned previously, several experimental findings support the common activation of brain regions while remembering the past and imagining the future, demonstrating that similar processes support both activities. For example, Okuda and colleagues (2003) showed that some brain areas, such as the superior frontal gyrus and parahippocampal gyrus, showed equivalent level of activations during imagining the future and remembering the past. Additionally, common networks were found to underlie past and future events during construction and elaboration phases (Addis et al., 2007). Participants were required to recall a past event or imagine a future event in two phases, construction and elaboration. In the construction phase, individuals searched for and re/constructed past and future events, and once they had an event in mind, in a subsequent elaboration phase, they retrieved or imagined supplementary details. Authors employed functional magnetic resonance imaging (fMRI) to examine patterns of neural activity associated with the construction and subsequent elaboration phases of past and future events. During the construction phase past and future events recruited commonly hippocampus, inferior parietal lobule, middle occipital gyrus, and superior occipital gyrus/cuneus. On the other hand, the elaboration of past and future events was associated with the activation of the frontopolar and inferior parts of the mPFC (BAs 10 and 11), temporal pole and middle temporal gyrus, hippocampus, parahippocampal gyrus, cingulate/retrosplenial regions, precuneus, and inferior parietal lobule. Moreover, in the study by Szpunar et al. (2010) we mentioned previously, the acts of envisioning the future and remembering the past revealed identical timecourses of activation in the mPFC, posterior cingulate cortex, medial temporal cortex, and occipital cortex.

Despite the common brain activity that occurs while remembering the past and imagining the future, there is also evidence about possible asymmetries when the two abilities are compared with each other. For instance, it was demonstrated that prefrontal and medial temporal areas show increases in activity while imagining the future relative to recollecting the past (Okuda et al., 2003). Moreover, Addis and colleagues (2007) revealed that the maximal difference in brain activation for past vs. future events was found in the event construction phase. Great activity was found in the frontal pole and the hippocampus during the construction of future events relative to the construction of past experiences. Also Szpunar et al. (2007) showed several regions that were more active for future compared to past events (but not vice versa), such as middle frontal gyrus, medial posterior parietal cortex, and posterior cerebellum. Altogether these results suggest that within the core network of brain regions that is commonly engaged in remembering the past and imagining the future some areas may support preferentially only one aspect of MTT, for instance, the ability to simulate novel experiences.

The constructive episodic simulation hypothesis (see 2.1) may explain the greater neural activity for future relative to past events. It may reflect the more extensive constructive processes required by imagining future events relative to remembering past events (Addis et al., 2009a; Schacter et al., 2012). Indeed, imagining future experiences requires that details derived from past experiences are recombined to construct a novel future experience, which increases cognitive demands compared to just recall already happened events.

Together, these studies suggest that remembering the past and imagining the future are based on similar processes and share neural substrates. A fronto-temporo-parietal network of brain regions, including the mPFC, shows activation during both remembering the past and imagining the future and this network has commonalities with the DMN. However, differences in brain activity that emerged in imagining the future and remembering the past may suggest that some brain areas, for example frontal regions and the hippocampus, are more engaged while imagining future events. Evidence for similarities and differences in remembering the past and imagining the future was shown also in clinical studies, which is the topic of the next paragraph.

2.3 Neural bases of remembering the past and imagining the future: clinical studies

Additional evidence for the common neural bases of episodic memory and future thinking comes from neuropsychological studies on patients. It is well known that patients with damage to the hippocampus and related structures in the MTL have impairments in episodic memory (e.g., Squire, Stark, & Clark, 2004). For example, patients with MTL and/or hippocampal damage have often intact perceptual abilities and intellectual functions, however, they may be amnesic and have severe deficits at recalling events from their past. For example, when patients with MTL lesions are asked to retrieve and describe past events, their recall episodes were lacking in detail when compared to healthy participants (e.g., Race et al., 2011). Tulving (1985, 2002) presented the case of an amnesic patient, K.C., who suffered from severe amnesia due to the result of closed head injury, which had produced damage to a number of brain regions including the medial temporal and frontal lobes. Patient K.C. had intact general personal knowledge, for instance he could remember the names of the schools he attended, and he had also intact non-personal knowledge, so that he could describe how the Statue of Liberty looked like. Interestingly, his amnesia was present with a parallel deficit in imagining personal future experiences. For instance, when the experimenter asked K.C. what he would be doing the following day, he answered that he did not know, and declared that his mind was completely blank. Another famous case of memory loss, patient D.B., supports the hypothesis that episodic memory is the foundation that allows to imagine the future (Klein et al., 2002). Patient D.B, who received a diagnosis of cardiac arrest with presumed anoxic encephalopathy, had a deep difficulty in remembering events and imagining what his experiences might be like in the future, but retained the ability to think about non-personal past and future events. In particular, patient D.B. and healthy participants were presented with words and were asked to think of a specific personal event related to each word from any time in their past. They were instructed to provide a brief verbal description of each memory and to date the memory as accurately as possible. Patient D.B. was unable to recollect experiences from any point in his life. Moreover, a questionnaire requiring participants to recollect personal events from their past and to imagine personal events in their future was administered. D.B.'s episodic impairment was reflected in his performance on both the past and future versions of this task. Patient D.B. was often not able to provide an answer, and the few answers he provided were judged implausible. For example, D.B. stated that he was going to visit his mother, who in fact had died almost 20 years earlier. Finally, participants in the same study were asked to focus on public domain issues: they were asked to describe events that had taken place during the past 10 years, and events they believed likely to take place over the next 10 years. D.B.'s responses were judged correct and plausible, suggesting intact ability to recall and imagine novel non-personal general events (Klein et al., 2002). Once again, a patient was described with intact general knowledge about events, however, he was not able to recall personal specific episodes and to imagine personal future experiences, similarly to patient K.C. In another study by Andelman and colleagues (Andelman et al., 2010), patient M.C., with bilateral hippocampal damage, was found to have difficulties in recalling personal past events, especially events occurred in the last years. To assess the patient's ability to imagine future experiences the same questionnaire on personal future events used by Klein and colleagues (2002) was administered. Patient M.C. exhibited persistent difficulties in the ability to envision and plan for her personal future. However, her general knowledge and semantic memory were intact. Interestingly, a study published by Hassabis and colleagues (2007b) showed that amnesic patients, with bilateral hippocampal damage, not only have difficulties at imagining future episodes, but also at imagining novel fictitious, atemporal experiences. Indeed, the authors found that amnesic patients were impaired, compared to healthy controls, at imagining and descripting any novel scenario. Descriptions of the constructed experiences provided by participants were scored across a number of ratings to assess their event construction richness. A composite score that measured the overall richness of the imagined experience was calculated from four subcomponents: information content (number of details for each event), participants' ratings on sense of presence and vividness, a spatial coherence index (assessing the spatial integrity of the imagined scene), and a scorer's rating on the overall quality of the constructed experiences. Hippocampal patients' descriptions were fragmented and lacked spatial coherence: patients showed a diminished overall quality of the constructed experiences and also a decreased spatial coherence index compared to healthy controls in both future and fictitious experiences. Thus, hippocampal amnesia causes a deficit in imagining new experiences and authors pointed out that the role of the hippocampus extends beyond reliving past experiences, encompassing not only the imagination of future experiences, but more generally, it is engaged in the construction of fictitious experiences. The hippocampus may support scene construction, which is the ability to create and maintain spatial coherent complex scenes (see paragraph 2.1). In the literature, other clinical studies revealed parallel deficits in remembering the past and imagining the future in patients with MTL lesions. For instance, Race and colleagues (2011) found that amnesic patients with MTL damage were impaired at constructing detailed narratives about personal past and future events. Patients and healthy participants were required to recollect specific personal events from the past (e.g., graduation ceremony) and imagine specific personal events in the future (e.g., winning the lottery). Participants were instructed to describe the event in as much detail as possible. In another condition, participants were shown drawings of scenes and they were instructed to tell a story about what was going on in the scene. Narratives were scored using the Autobiographical Interview scoring (Levine et al., 2002): narratives were segmented into distinct details and then each detail was categorized as an episodic detail or a non-episodic detail (semantic, repetitions, and meta-comments). Episodic details are those that pertained directly to the main event described by the participants, they are specific to time and place, and are considered to reflect episodic re-experiencing. Non-episodic details do not belong to specific episodes and depict general knowledge and facts, ongoing events, and extended states of being. Amnesic patients with MTL damage were impaired at constructing detailed narratives about personal past and future events producing fewer episodic details compared to those provided by healthy participants. Moreover, future thinking performance correlated with episodic memory performance, showing an association between episodic memory and EFT. However, MTL patients possessed preserved ability to construct narratives (i.e., describe the content of pictures verbally) (Race et al., 2011), suggesting that MTL patients impairment is not associated with a general deficit in narrative abilities (Race et al., 2013; but see Zeman et al., 2013). Different results were found by Squire et al. (2010), who examined patients with amnesia (hippocampal and MTL lesions) and healthy participants. They administered an adapted version of the Autobiographical Interview (Levine et al., 2002) to patients with hippocampal damage, one MTL patient, and healthy controls. The authors evaluated their capacity for constructing autobiographical memories and future experiences (remote and recent memories, and episodes that may occur in the near future). They found that the episodic recall of recent events was affected in amnesic patients with hippocampal lesions and in the patient with MTL lesion compared to healthy participants, however, the recall of remote events and the imagination of future episodes were preserved in patients, suggesting that those abilities may depend on other brain structures than the MTL.

Indeed, other brain structures have been found to support MTT. The frontal lobes were hypothesized to support autonoetic consciousness (Wheeler et al., 1997), a process considered necessary for remembering the past and imagining the future (see 2.1 and 2.2). It is interesting to note that patient K.C., the clinical case we mentioned before, who showed impaired ability to recall personal past experience and imagine personal future events, had extensive lesions not only in the medial-temporal areas but also in the frontal lobes. In a study on patients with traumatic brain injury (TBI), participants were instructed to recall or imagine events from different time periods (1 month, 5 years, and 10 years). Recalled and imagined events were scored following the Autobiographical Interview scoring (Levine et al., 2002). TBI patients recalled and imagined fewer episodic details compared to those recalled and imagined by healthy controls, reflecting impaired episodic memory and impaired EFT. In contrast, semantic details were unimpaired in TBI patients' simulation of past and future events. These results suggest the involvement of the prefrontal cortex in episodic memory and EFT (Rasmussen and Berntsen, 2014). Other studies show that the ventral part of the prefrontal cortex may be specifically involved in MTT. Levine (2004) described patients with ventral prefrontal damage who were impaired, relative to controls, in remembering personal past episodes. Patients' reports lacked in episodic details, but contained a normal number of non-episodic details. On the other hand, patients with dorsolateral prefrontal damage produced similar amount of episodic details compared to controls, but an elevated amount of non-episodic details. These findings demonstrate a possible specific involvement of the ventral part of the frontal lobe in retrieving specific past episodes, however, in that study EFT was not assessed. In other studies, Levine et al. (Levine et al., 1998a, 1998b) described patient M.L., who suffered damage to the right ventral frontal cortex after a TBI. Patient M.L. developed retrograde amnesia for episodic and semantic information and M.L.'s impaired abilities encompassed also strategy application that has been linked to self-regulation and EFT (Atance and O'Neill, 2001). A further evidence of possible memory impairment in patients with damage to the ventral part of the mPFC is that they may exhibit a particular disorder of memory, named "confabulation", involving false recall and recognition of events that did not actually happen (Kopelman, 1987; Gilboa and Moscovitch, 2002; Gilboa et al., 2006). Interestingly, confabulation may also involve EFT. For example, Dalla Barba and colleagues (1997) reported a case of a patient, who developed an amnesic-confabulatory syndrome following a rupture of an aneurism of the ACoA. Evaluation showed that patient's confabulations were related to tasks requiring to access personal past or personal future events (see also Cole et al., 2014). For instance, when the experimenter asked patient G.A. what she will be doing tomorrow, she answered she will go shopping alone by car, but she actually never did that after her disease. These findings demonstrate, again, a link between remembering events and imagining future episodes in a disorder specifically related to the frontal lobes: confabulation that is typically present in past events but may emerge also in EFT.

It is important to note that not all studies on the involvement of frontal lobes in MTT show the same parallelism between remembering the past and imagining future experiences. An example of asymmetry in the performance of simulating past and future events is the study by de Vito et al. (2012). They investigated non-amnesic patients with Parkinson's Disease (PD), who might have a mild cognitive deficit, in order to understand whether they possess a future thinking deficit. PD patients underwent assessment of the frontal lobe functions, by the mean of the Frontal Assessment Battery, in order to study a possible link between executive abilities and EFT. PD patients showed a decrement in episodic details when imagining future experiences but not when remembering past events. PD patients in this study performed normally also in constructing fictitious novel scenarios. Interestingly, EFT deficit was associated with score on the sensitivity to interference task, a test included in the Frontal Assessment Battery. The authors pointed out that the involvement of executive functions in the generation of episodic future experiences may suggest a specific involvement of the frontal lobe in EFT. Moreover, this study shows that future thinking deficits does not represent a specific feature of amnesia. Another experiment demonstrating a differential engagement of brain regions in MTT studied cases of frontotemporal dementia. In patients with behavioral variant of frontotemporal dementia, deficits were found in imagining the future and remembering the past. However, performance in remembering past events and imagining future episodes correlates with the degree of atrophy in distinct brain regions: disruption of future thinking correlates with atrophy of frontopolar, medial temporal regions, and lateral temporal and occipital cortices, on the other hand, remembering deficit correlated with atrophy in medial prefrontal regions (Irish et al., 2013). Weiler and colleagues (2010) described two patients with lesions in the medial dorsal thalamus, which is densely connected with prefrontal cortex, who could remember personal past events but had difficulties imagining future events. The authors attributed this finding to the increased strategic retrieval/recombination demands of EFT compared to remembering (Weiler et al., 2011). Interestingly, patients' deficits were even more marked when they had to imagine events happening to other people (e.g., Angela Merkel), which may require retrieving/recombining details from more, and more disparate, memories (Weiler et al., 2011). Again, these results show the possible involvement of prefrontal areas in supporting MTT and suggest that different brain regions within the prefrontal cortex may underlie different component processes of MTT. Consistently with the aforementioned literature, it has been hypothesized that the frontal cortex has the specific role in allowing individuals to anticipate and plan the future (Ingvar, 1985; Atance and O'Neill, 2001; Fuster, 2008). For instance, patient R. with a frontal lobe lesion, described by Stuss (1991), showed intact general knowledge about the future, however, she was not able to use that knowledge for making decisions about her future (Atance and O'Neill, 2001). Furthermore, a lesion to the ventral part of the mPFC may be sufficient for provoking a disruption of decision making about the future, suggesting an inability to consider and anticipate future experiences. Research on patients with lesions to the vmPFC showed that patients appear "myopic" to the future consequences of their choices (Bechara et al., 1994). Bechara and colleagues created a gambling task requiring to choose cards from four decks, of which two led to a high initial gain of money, followed by higher losses (disadvantageous decks). Choosing cards from the other two decks resulted in a small immediate gain, followed by smaller unpredictable losses. Patients with lesions to the vmPFC tend to select more cards from the disadvantageous decks. vmPFC patients were described as insensitive for future consequences because they were guided by immediate outcomes. In another study (Fellows and Farah, 2005) patients with lesion to vmPFC showed a short future time perspective: they tended to conceive future events closer in time compared to events imagined by healthy and brain-damaged controls. Indeed, personal future time perspective was reduced following vmPFC damage, while participants with dorsolateral prefrontal damage did not differ from controls, suggesting that the shortened future time perspective is a specific consequence of a lesion to the vmPFC. In another study vmPFC patients showed steeper Temporal Discounting (TD) than healthy and brain-damaged controls (Sellitto et al., 2010). In this last study, participants chose between an amount of a reward that could be received immediately and an amount of reward that could be received after some specified delay. Lesions to the vmPFC increased preference for small-immediate over larger-delayed rewards compared to healthy controls and patients with lesion to non-frontal areas. These results may be due to vmPFC patients inability to envision future experiences, which would lead to prefer the more salient immediate reward. vmPFC patients would be deprived of the anticipation of the future reward that is necessary for decision-making (Ciaramelli and di Pellegrino, 2011). Together these findings show that when the frontal damage encroaches the ventral part of the mPFC, this can affect the ability to make effective future decisions and may provoke a decreased capability to anticipate future experiences.

Other studies showed also a possible involvement of the parietal lobe in supporting MTT. Berryhill and colleagues (Berryhill et al., 2007) evaluated autobiographical memory in patients with bilateral parietal lesions and they showed that the patients' recollections lacked richness and specificity when they were asked to recall freely memories from different points in time (free recall). In contrast, the patients were not impaired in their ability to answer specific questions regarding particular memories. In a subsequent study, Berryhill et al. (2010) examined autobiographical memory, EFT and imagination of atemporal experiences in patients with bilateral posterior parietal lesions (PPC patients) and unilateral prefrontal lesions (PFC patients). PPC patients exhibited free recall impairment in remembering autobiographical episodes, replicating previous findings, and they showed also impaired performance in imagining future and fictitious experiences. These results suggest that the parietal lobe is important for constructing any kind of complex experiences, irrespectively of the temporal feature. On the other end, the PFC patients (with unilateral lesions) demonstrated intact autobiographical memory retrieval but impaired construction of future and fictitious experiences, suggesting an involvement of the prefrontal cortex in constructing novel experiences, but not in episodic memory. On the whole, these results in clinical populations confirmed empirical findings from neuroimaging studies (see 2.2) and consolidate the idea about the involvement of a set of brain regions in deliberate MTT, including temporal, frontal, and parietal brain areas (Buckner and Carroll, 2007; Hassabis and Maguire, 2007, 2009; Schacter et al., 2012). Some studies (e.g., Berryhill et al., 2010; de Vito et al., 2012; Irish et al., 2013; Weiler et al., 2011) that showed the differential engagement of brain regions in remembering past events and imagining future experiences, raise questions about what brain areas may support specifically only the simulation of future or, alternatively, the retrieval of past events. Until this point the characteristics of deliberate MTT have been delineated, however, MTT may also occurs spontaneously, for example during mind wandering. The next sections are dedicated to the conceptualization and the neural bases of mind wandering.

3 Mind wandering

3.1 Mind wandering: theoretical concepts

Individuals’ minds tend to wander and produce thoughts that are self-generated, and typically related to inner experiences, without a clear link with the perceptual external environment (Smallwood and Schooler, 2006, 2015; Andrews-Hanna et al., 2014). Inner experiences of self-generated thoughts may be task-related or task-unrelated. Thus, these experiences can occur as part of a task (task-related), for instance making a task-related decision that depends on an internal representation. More frequently, they can happen independently from a task (task-unrelated), such as when individuals mind-wander while performing an activity, or while resting without any task to perform (Andrews-Hanna et al., 2014; Smallwood and Schooler, 2015). During mind wandering individuals' minds drift away from the ongoing task toward inner thoughts, fantasies, and feelings unrelated to the task at hand (Smallwood and Schooler, 2006). For example, while washing the dishes one may think spontaneously about going shopping the day after. It is important to underline that mind wandering is not an external distraction, such as, while performing a task our attention focuses on a phone that is ringing (external stimulus). An external distraction, even if it is not a thought related to the task, it is not self-generated but it is guided by external perception (Smallwood and Schooler, 2006, 2015; Schooler et al., 2011). Therefore, mind wandering experiences are not derived directly from an external stimulus, they form a train of endogenous thoughts (Smallwood and Andrews-Hanna, 2013).

Because mind wandering is so evanescent and independent from external stimuli specific methods to study this phenomenon have been carefully developed. A common method for investigating mind wandering is thought sampling, that is the assessment of the inner experience of an individual as he or she is completing an experimental task. The measures of mind wandering used in empirical investigations can be grouped into two categories: probe-caught mind wandering and self-caught mind wandering. In probe-caught mind wandering, individuals are interrupted during the performance of a task and asked to report their experiences. These probe-caught mind wandering episodes can be recorded using a computer or through a verbal report. Probe-caught measures were used to examine mind wandering with two different methods. In the first method, the individual is trained to recognize an example of mind wandering and he or she is probed throughout a task to determine whether mind wandering episodes occur using yes/no judgments (e.g., Schooler et al., 2005). A second method requires participants to report what was passing through their mind right before the thought probe. These verbal reports are recorded and can be coded by the experimenters on whether they are on-task (task-related) or off-task thoughts (mind wandering) (Smallwood et al., 2003). On the other hand, in self-caught mind wandering, participants are asked to monitor their awareness for off-task thoughts and to report whenever mind wandering episodes occur (Cunningham et al., 2000). Self-caught mind wandering requires individuals to become aware of the content of their inner experiences while doing a task. Another way to collect mind wandering experiences is the retrospective method. The data are collected at the end of a task by the use of questionnaires, without interruption of the natural course of the task (e.g., Barron et al., 2011). Finally, an open-ended method can also be employed to collect data on mind wandering experiences by asking participants to describe in their own words what they experienced during a task (Baird et al., 2011) without imposing categories that constrain participants' reports (Smallwood and Schooler, 2015). Mind wandering experiences can also be probed in ecological settings.

For example, participants can be asked to carry pagers during their day. An individual's experience is sampled at random intervals through an electronic device (e.g., Killingsworth and Gilbert, 2010). When probed, the participant is asked to describe thoughts, providing details on the nature of the inner experience (Smallwood and Schooler, 2006)

Our daily lives are rich with thoughts that emerge without a direct relationship to the here and now. This phenomenon occurs often and occupies an high amount of time during daily life, around 30% of the awaking hours (Kane et al., 2007; Killingsworth and Gilbert, 2010). In a study about the contents of mind wandering (Delamillieure et al., 2010) authors found that inner experiences of participants during rest, while participants were asked to let their thoughts come and go, indicate a dominance of mental imagery and inner speech. A majority of participants reported retrospective memories or prospective thoughts, or both, suggesting that when participants were let to think freely they often produced spontaneous memories and future-related thoughts. The contents of mind wandering episodes involved often thoughts that allow individuals to escape from the here and now, therefore, they are often temporally-related, and even more often future-related (Smallwood et al., 2009, 2011b; Song and Wang, 2012). For instance, it has been demonstrated that when engaged in a task low in cognitive demands, for example tasks with a low demands on working memory or attentional resources, individuals are more prone to experience mind wandering about the future. In one experiment, Smallwood and colleagues (2009) asked participants to perform three computerized tasks in which numbers were presented one by one. Participants performed a choice reaction time (CRT) task during which they were asked to determine whether the stimulus was odd or even. They underwent a working memory task in which they were required to indicate whether the number presented before a target stimulus had been odd or even. Moreover, they were also asked to perform a passive viewing task, during which they watched numeric digits appearing on the screen. During all tasks, they were asked to describe their mental state at thought probes and classified the temporal focus of their thoughts. Participants showed a prospective bias: they experienced high frequency of thoughts about the future whenever the task environment allowed them sufficient attentional resources to do it. These results suggested that mind wandering towards the future needs additional resources to occur and these resources are used when they are available, that is, when the current task is not demanding. A study about mind wandering experience in Chinese participants demonstrated how phenomenology of mind wandering is similarly also across different cultures (Song and Wang, 2012). In that study, authors used a questionnaire to investigate mind wandering experiences during daily life through probes appearing on participants' mobile phones. Participants had to indicate whether they were mind-wandered and answer questions about mind wandering experiences' characteristics, for example, the contents of mind wandering in terms of episodic or semantic components and temporal orientation of thoughts. Among Chinese participants, the episodic mind wandering had the highest proportion and the results showed that episodic mind wandering was future biased: the future-oriented episodes were more frequent than those with other time-orientations. Another study investigated contents of mind wandering (Stawarczyk et al., 2013). Authors studied mind wandering with thought-probes during the Sustained Attention to Response Task (SART; Robertson et al., 1997). During SART, non-target stimuli were presented, one stimulus at a time, and participants were required to respond manually to each non-target stimulus. Sometimes, a target stimulus was presented and it required a manual response to be retained. SART was divided in different blocks and mind wandering was assessed after each block. After the SART completion, participants were asked to rate each mind wandering episode on various dimensions, including their representational format, structuration and intentional aspect, repetitiveness, abstractness, and emotional valence. On average, mind wandering episodes involved a moderate amount of visual imagery and inner speech, they did not belong to a structured sequence of thoughts and their occurrence was not intended. Moreover, mind wandering content was mostly realistic and concrete, and moderately important. Finally, most of the reported mind wandering episodes did not involve thoughts that occur repetitively, and their affective content was neutral. In particular, their results show that future-oriented mind wandering episodes, which were more frequent than other temporal categories, involve inner speech and are more self-relevant, concrete, structured, and intended than non-future-oriented mind wandering episodes. Together, these results demonstrate the consistency of the prospection bias across studies that investigate mind wandering and show also the variety of characteristics of mind wandering experiences across participants and experiments.

3.1.1 Psychological hypotheses of mind wandering

There are four main psychological hypotheses that can explain the occurrence of mind wandering: the current concerns hypothesis, the decoupling hypothesis, the executive failure hypothesis, and the meta-awareness hypothesis (Smallwood, 2013).

The current concerns hypothesis argues that the experience of mind wandering occurs because the individual has goals, wishes, and desires that are not related to the perceptual current moment. Thus, mental life is guided by salient experiences, and whenever the current environment lacked of salient information, self-generated thoughts emerge. In a situation where the environment is full of salient perceptual information, for example while listening to an interesting and engaging talk, external events guide the attention to perception (Klinger et al., 1973). Automatic processing of current concerns may produce the content of mind wandering. Current concerns are processes active during the time one has a goal, those concerns may trigger the engagement in mind wandering, so that the main goal of an individual changes from paying attention to the current environment to thinking of a personal relevant goal, for example, when an individual imagine to go to the mall and to buy a necessary item while he or she is washing the dishes (Smallwood and Schooler, 2006).

A second hypothesis that explain mind wandering is the decoupling hypothesis. It assumes that certain mental processes are common to self-generated and externally maintained trains of thought (Antrobus et al., 1970; Teasdale et al., 1995; Smallwood and Schooler, 2006). Mental processes are described as decoupled when the beginning of their activity is not directly related to an external event. Mental processes can serve overlapping functions during self- and externally triggered thoughts. For example, the process of executive control can help the maintenance of self-generated thought similarly to when it maintains cognition guided by an external task (Smallwood et al., 2007). The decoupling hypothesis assumes that executive resources, which can maintain also attention to the external environment, are useful to support the continuity of an internal train of thoughts (Teasdale et al., 1995; Smallwood and Schooler, 2006; Smallwood et al., 2012). Evidence for this hypothesis come from studies on spontaneous thoughts and their relation with the disruption of sensory external attention. When mind wandering occurs attention to the external stimuli diminishes, suggesting that mind wandering may “steal” executive resources from the external environment in order to survive (Mcvay and Kane, 2010; Smallwood et al., 2011a). For example, in a study by Smallwood and colleagues (2008) participants performed a computerized SART divided in blocks. At the end of each block of stimuli a thought probe was presented to collect on-task and off-task (mind wandering) experiences. Event-related potentials, generated by the non-target stimuli as a function of whether they preceded a marker of mind wandering or on-task experiences, were recorded. Authors found evidence that when the mind wanders there is a reduction in the cognitive analysis applied to the task. In particular, the amplitude of the P300, that is an index of the amount of attentional resources directed towards a stimulus, was reduced for non-targets presented during mind wandering compared to periods during which participants’ thoughts were classified as on-task. These results show that during mind wandering attentional resources are less directed to the task, and are employed instead to support mind wandering.

The executive failure hypothesis proposes that mind wandering is a form of distraction and when the attention control system fails to maintain attention to the task, self-generated information unrelated to the task may become prevalent. This hypothesis proposes that mind wandering reflects a failure of the executive-control system to adequately fight interfering thoughts that are generated and maintained automatically (Mcvay and Kane, 2009, 2010). Mcvay and Kane argued that if mind wandering demands resources, as it is hypothesized by the decoupling hypothesis, individuals with greater resources, for example working memory capacity, should mind-wander more often than do those with fewer resources. However, Mcvay and Kane found that people with high working memory capacity reported mind wandering less frequently during demanding tasks than do individuals with low working memory capacity (Mcvay and Kane, 2009), suggesting that greater working memory resources may help individuals to be less prone to distractions, and so less prone to mind wandering, and more engaged in the current task.

Another hypothesis argues that meta-awareness, that is the capacity to have explicit knowledge of the current contents of consciousness, is an important process related to mind wandering (Schooler, 2002; Smallwood and Schooler, 2006; Schooler et al., 2011). The meta-awareness hypothesis points out that the capacity to represent the contents of consciousness allows the individual to identify conscious thoughts that deviate from the desired goal. One possibility is that meta-awareness can help the identification of mind wandering and the consequent re-engagement of the attention to the main task (Schooler et al., 2011). This happens, for example, during meditation, when dynamic fluctuations between states of being focused on meditation and mind wandering occur. Meta-awareness may be critical for catching the mind engaged in a wandering state and for re-directing the attention to a meditative condition (Schooler et al., 2011; Hasenkamp et al., 2012). Another possibility is that meta-awareness does not contribute to the end of mind wandering episodes, that may terminate for other reasons such as for an external stimulus, but meta-awareness aids to reconstruct previous conscious experiences (inner cognition) retrospectively. After having delineated the processes that may maintain and regulate the mind wandering, to better understand this phenomenon it is necessary to spend few words for explaining which the possible advantages and disadvantages of engaging in mind wandering are.

3.1.2 The costs and benefits of mind wandering

Studies suggest that mind wandering produces costs and benefits for individuals (Mooneyham and Schooler, 2013; Smallwood and Schooler, 2015). For instance, while individuals read they may report a high incidence of mind wandering episodes. When participants are asked to read a text and are periodically probed with questions regarding whether their thoughts are on or off-task, mind wandering frequency correlates negatively with reading comprehension (e.g, Schooler et al., 2005). As we mentioned before, a task typically used to collect mind wandering experiences is the SART (Robertson et al., 1997), during which thought probes are presented asking participants to report and classify their thoughts. The effects of mind wandering during performance of the SART can be observed by examining errors and reaction times. Mind wandering rates are correlated with SART errors, variability on reaction times, and omissions (Allan Cheyne et al., 2009). Therefore, mind wandering might provoke errors of sustained attention, such as failing to notice an infrequent target. Moreover, mind wandering disrupts performance also in tests of working memory. In one experiment by Mrazek et al. (2012) participants completed versions of the operation span task (OSPAN), reading span task (RSPAN), and symmetry span task (SSPAN). Participants completed the three tasks during which sets of letters to be remembered were presented in alternation with a secondary unrelated task (secondary tasks consisted of: verifying the accuracy of an equation for OSPAN, verifying the meaningfulness of a sentence for RSPAN, and verifying the vertical symmetry of an image for SSPAN). Mind wandering was assessed during each span task. Authors showed that performance on each task was negatively correlated with the number of mind wandering episodes occurring during the task. Together, these results demonstrate that mind wandering disrupts performance in tasks of different nature.

On the other hand, producing thoughts unrelated to the task at hand may help individuals in some circumstances. The self-generated thoughts that occur during mind wandering are often focused on the future, as we mentioned previously, hence, a function of mind wandering may be the anticipation and planning of personal relevant future goals (Baumeister and Masicampo, 2010). Thus, thinking about the future will permit individuals to be prepared to future aims, to overcome future obstacles, and to make effective decisions. Another advantageous effect of mind wandering is the ability to generate creative thoughts. For instance, Baird and colleagues (2012) studied the relation between mind wandering and creative thinking. Participants were required to generate as many unusual uses as possible for a common object, such as a brick, in a certain amount of time (Unusual Uses Task, UUT). After completing the baseline UUT, participants were assigned to one of four conditions. In three conditions the baseline UUT was followed by an incubation period. During the incubation period, one group of participants performed a demanding 1-back working memory task, in a second condition participants performed an undemanding CRT task (0-back) requiring infrequent responses and in another condition participant were asked to rest. In the fourth condition participants did not receive any break between sessions. Next, the UUT task was repeated in all four condition (either after the break or right after the baseline). In all conditions, after the break mind wandering was assessed. The study demonstrated that taking a break involving an undemanding task, during which more mind wandering episodes occurred, improved creativity more than did taking a break involving a demanding task, resting, or taking no break. The authors argued it is possible that specific kinds of unrelated thoughts may facilitate creative problem solving. Another possible positive effect of mind wandering is to allow individuals to place their experience in a meaningful context, thus, they can integrate experiences into a meaningful narrative. For instance, mental simulation have been linked to enhanced life meaning. Simulating mental experiences that transcend the here and now may induce individuals to increase the sense of coherence and meaning of their own life (Waytz et al., 2015). Finally, mind wandering may also be useful by providing mental breaks to overcome monotonous tasks (Mooneyham and Schooler, 2013; Smallwood and Schooler, 2015).

Now that the characteristics of mind wandering have been described it is critical to know which brain regions support mind wandering.

3.2 Neural bases of mind wandering

Initial investigation on the neural bases of mind wandering comes from two experiments by McGuire, Paulesu, Frackowiak, and Frith (1996). In those two experiments participants performed language tasks. In a first study participants were asked to perform overt and silent articulations and tongue movements, or they were asked to rest and empty their minds. In a second study, participants read single words silently, aloud or they read words aloud while another person was saying the words. In both studies, immediately after each scan, subjects were asked to rate the frequency of thoughts unrelated to the task or unrelated to their immediate environment (mind wandering). The authors demonstrated that the frequency of mind wandering experienced during the scans correlated mainly with mPFC activity and also with the inferior temporal gyrus activity, estimated using positron emission tomography (PET) scans. After that, other studies explored the relationship between mind wandering and brain activity using magnetic resonance imagining (MRI) techniques. For instance, a study revealed that rest (during which an high frequency of stimulus unrelated thoughts was found), as compared to a tone detection task, was associated with increased activity in many brain regions mainly in the left hemisphere, such as the orbital frontal and rostral-ventral anterior cingulate cortex, dorsal prefrontal cortex, parahippocampus, angular gyrus, posterior cingulate/retrosplenial cortex. Authors hypothesized that during rest individuals may track the passage of time, plan future actions, or retrieve episodic information (Binder et al., 1999). In another study (McKiernan et al., 2003, 2006), the frequency of mind wandering experiences was collected during an auditory target detection task in a mock scan. Task difficulty was manipulated within each of three factors: stimulus presentation rate, target discriminability, and memory load. It has been shown that during tasks composed by targets easy to detect participants produced about twice thoughts unrelated to the task compared to a more difficult task (targets difficult to detect). In this study, correlations between mind wandering frequency and brain deactivation induced by the task were calculated, which revealed strong correlations in the posterior parieto-occipital cortex, fusiform gyrus, anterior cingulate gyrus, and middle frontal gyrus. The authors interpreted the results suggesting that those brain regions are engaged in cognitive processing during resting conditions, and this cognitive processing is interrupted in the presence of an exogenous task (McKiernan et al., 2003, 2006). An important study on mind wandering, which linked mind wandering to the DMN activity, revealed a significant positive correlation between the frequency of mind wandering and the change in blood-oxygen-level dependent signal in several regions observed when participants performed practiced (high incidence of mind wandering) compared to novel blocks (Mason et al., 2007). To investigate the relation between brain activity and mind wandering, the authors trained participants on blocks of verbal and visuospatial working-memory tasks (practiced blocks). Moreover, some other new blocks were administered (novel blocks). The verbal working memory task involved remembering and manipulating 4-letter sequences. After a 4-letter sequence was displayed, an arrow indicated if the string should be referenced in the forward or backward direction. The participants were then prompted by the appearance of one of the four letters contained in the string and they were to indicate the position at which the letter appeared in the string displayed before. The visuospatial task involved remembering and manipulating finger-tapping patterns. A key-press sequence to follow was displayed and it was indicated whether the key-press sequence should be performed in the forward or backward direction. Among trials a fixation was displayed (baseline). Proportion of thoughts participants classified as mind wandering varied by block type (baseline, practiced, or novel): participants reported a greater proportion of mind wandering experiences during the baseline blocks than during both practiced blocks and novel blocks. Participants reported a significantly greater proportion of mind wandering experiences during the practiced blocks than during the novel blocks. fMRI results showed that activity in brain regions belonging to the DMN was greater during high-incidence of mind wandering periods. Activation was found in the mPFC, superior frontal gyri, anterior cingulate, posterior cingulate, precuneus, angular gyrus, insula, superior temporal, and middle temporal gyri. These findings demonstrated that activity observed in the DMN is associated with mind wandering and that reductions in processing demands, performing practiced versus novel sequences, were accompanied by an increment in both mind wandering and in activity of the DMN (Mason et al., 2007). Consistent results about the involvement of DMN in mind wandering come also from other experiments (Christoff et al., 2009; Stawarczyk et al., 2011). In particular, Christoff and colleagues explored the brain recruitment that occurs when the mind wanders away from the main task asking participants to report also how aware they were about the mind wandering experience. To collect mind wandering reports participants were presented with thought probes while performing a SART. Each thought probe asked subjects two questions: whether their attention was focused on the task or off-task, and whether or not they were aware of where their attention was focused. Unawareness was defined to subjects as the experience of not recognizing that mind wandering had occurred until the probe was presented. The interval of time directly preceding a probe was classified as on-task or off-task according to participants' response to the thought probe. Off-task intervals were divided into mind wandering with meta-awareness and mind wandering in the absence of meta-awareness. Errors in SART provided a behavioral index of mind wandering, hence, the interval preceding each target was categorized according to the subject's response as either correct or incorrect. During episodes of mind wandering (off-task thoughts), compared with episodes of being on-task, the recruitment of both default and executive network regions was observed. Activations were observed in the most prominent DMN regions, including the ventral anterior cingulate cortex (BA 24/32), the precuneus, and the temporoparietal junction. Also executive regions were activated: the dorsal anterior cingulate cortex and dorsolateral prefrontal cortex, temporopolar cortex, inferior and middle temporal gyri, anterior insula, and caudate nucleus, suggesting a processing overlap between mind wandering and central executive resources. Moreover, authors examined brain recruitment preceding errors. Activations were observed in DMN regions: the dorsomedial prefrontal cortex (dMPFC) and vmPFC (BAs 10 and 11). Both mind wandering and errors were preceded by activation in the DMN, suggesting a convergence between subjective and behavioral measures of mind wandering. Interestingly, brain recruitment in DMN and executive network was strongest when mind wandering occurred in the absence of meta-awareness. These findings demonstrate that mind wandering disrupts more task performance when it occurs without meta-awareness (Christoff et al., 2009).

An attempt to investigate different kind of cognition that occurs during mind wandering was performed by Stawarczky and colleagues (2011). They classified conscious experiences that can occur while participants perform a task requiring attention. In order to clarify the role of the brain activation in mind wandering compared to external attention, participants reported their experiences while they performed the SART. Thus, four possible responses to thought-probes were included, corresponding to the four classes of conscious experiences. Conscious experiences that can occur while performing a task were defined along two dimensions: task-relatedness and stimulus-dependency. These two dimensions define the classes of conscious experiences: task-related and stimulus-dependent (being completely focused on the current task), task-related and stimulus-independent (thoughts related to the appraisal of the task), task-unrelated and stimulus-dependent (external distractions), and task-unrelated and stimulus-independent (mind wandering). Authors found that reports of task-unrelated experiences (mind wandering and external distractions) were associated with increased activity in the mPFC, the posterior cingulate cortex, precuneus, and the posterior inferior parietal lobule, all regions within the DMN. Interestingly, increased activity in midline DMN regions was also associated with reports of stimulus-independent conscious experiences, independently of whether the content of these thoughts was related to the SART or not. Specifically, mind wandering episodes were associated with the highest degree of DMN activity but external distractions and task-related interferences (thoughts related to the appraisal of the task) were also associated with higher DMN activity compared to being focused on the task. This result suggests that these brain regions underlie cognitive processes active during both attention toward external stimuli and internal thoughts. Authors concluded that DMN is not a unified system but different regions may support different kind of cognition.

Together, these studies provided evidence for the importance of areas belonging to the DMN in supporting mind wandering. These regions partially overlap with those found to be involved in deliberate MTT, for example the mPFC, the posterior cingulate, and temporal areas. The next section will focus on the DMN, its discovery and its function in spontaneous and deliberate cognition.

4 The brain's default network (DMN)

The DMN is a set of brain regions in which activity increases when individuals are at rest or perform relatively undemanding tasks, for instance while they are fixating a cross on a computer screen. These regions are more activated during passive conditions than during an ongoing task. This can be interpreted as due to the fact that during rest individuals may perform some forms of mental operations that leads to brain activations (Shulman et al., 1997; Binder et al., 1999; Mazoyer et al., 2001; Raichle et al., 2001). The DMN was originally defined by patterns of deactivation during tasks of goal-directed cognition compared to passive conditions. The core regions that compose the DMN are vmPFC, posterior cingulate/retrosplenial cortex, inferior parietal lobule, lateral temporal cortex, dMPFC, and hippocampal formation (Buckner et al., 2008).

Attention was driven to the DMN's discovery in 2001 with papers written by Raichle and colleagues (Gusnard et al., 2001; Raichle et al., 2001). However, also before those papers, other authors explored the possibility that spontaneous thinking makes an important contribution to the rest state (Ingvar, 1985; Andreasen et al., 1995; Shulman et al., 1997). Ingvar (1985) and Andreasen et al. (1995) observed that the rest state was associated with dynamic mental activity (Buckner et al., 2008). It was suggested that the regions of the DMN are involved in remembering episodes, and planning (Andreasen et al., 1995; Binder et al., 1999). Later, it has been shown that the brain regions across the DMN were functionally related and they work in a coherent system (Greicius et al., 2003).

Studies have linked activity within the DMN to two main functions: monitoring of the external environment (the sentinel hypothesis) or internal mentation (Buckner et al., 2008; Andrews-Hanna, 2012). The sentinel hypothesis argues that passive conditions allow the individuals to monitor the external environment. It hypothesizes that activity within the DMN reflects attention to the external environment, when individuals monitor the environment for stimuli or significant events (Shulman et al., 1997; Gusnard and Raichle, 2001). A first evidence that supports this hypothesis is that task-induced deactivation in the DMN is most pronounced during tasks that involve foveal as compared to parafoveal or peripheral stimuli (Shulman et al., 1997). Secondly, under some circumstances, performance on sensory processing tasks correlates positively with DMN activity. Hahn et al. (2007), for example, observed that the DMN was linked to high levels of performance on a target-detection task but only for a diffuse attention condition where targets appeared at possible multiple locations, this result was not present when attention was cued to a specific location. These results suggest that regions within the DMN are active when attention focuses broadly on the environment and support the sentinel hypothesis.

However, in addition to broadly monitoring the external environment, during passive tasks participants commonly engage in internal cognitive processes, for instance, the generation of mental images, remembering past experiences, and simulating future situations. The internal mentation hypothesis suggests that the DMN permits self-reflective thought, which can activate medial prefrontal regions within the DMN (Buckner et al., 2008). In line with the idea that mPFC has a role in self-reflective processing, it has been found that imagining scenarios related to personal goals was associated with increased activity in ventral part of the mPFC relative to imagining non-personal experiences (Abraham et al., 2008; D'Argembeau et al., 2010b). vmPFC shows greater patterns of activation for self-related judgments relative to other-related judgments (van der Meer et al., 2010; Murray et al., 2012). In addition, the mPFC mediates the self-reference effect in memory tasks, that is the advantage to remember better self-related information than other-related information (Philippi et al., 2012). A damage to the mPFC abolishes the self-reference effect, suggesting that the mPFC may facilitate the representation of the self-relevance (Philippi et al., 2012). These results suggest an involvement of the mPFC, a key node of the DMN, in supporting thoughts that are self-reflective. The DMN also includes the hippocampal formation and regions that have been found important for supporting episodic remembering and EFT (see 2.2 and 2.3; Buckner and Carroll, 2007). It is possible, therefore, that the DMN underlies the ability to construct mental simulations. Andreasen et al. (1995) realized the correspondence between autobiographical memory and the DMN, showing that many regions of the DMN were active during autobiographical memory retrieval, including the vmPFC, dMPFC, posterior cingulate, inferior parietal lobe, lateral temporal cortex, and hippocampal formation (Maguire, 2001; Svodoba et al., 2006). Several studies reported the involvement of regions within the DMN not only in remembering the past, but also in imagining the future (see 2.2, 2.3; Addis et al., 2007; Botzung et al., 2008; Okuda et al., 2003; Szpunar et al., 2007). Moreover, regions within the DMN are active when individuals simulate other kind of mental experiences, for instance, when they take the perspective of others (see Spreng et al., 2009). The internal mentation hypothesis is also consistent with the functional fractionation of the DMN (Buckner et al., 2008). Indeed, Andrews-Hannah and colleagues (2010b) revealed distinct components of the DMN while participants were making personal decisions framed into the present or into the future. Firstly, in order to study the architecture of the DMN, intrinsic functional connectivity MRI was used to extract low-frequency spontaneous blood oxygenation level-dependent fluctuations within a set of a priori DMN regions. The results revealed that a core set of regions, including posterior cingulate cortex and anterior medial prefrontal cortex, is linked to two separate subsystems. One subsystem, named the dorsal medial prefrontal cortex (dMPFC) subsystem, includes the dMPFC, temporoparietal junction, lateral temporal cortex, and temporal pole. The second subsystem, called the medial temporal lobe (MTL) subsystem, includes the vmPFC, posterior inferior parietal lobule, retrosplenial cortex, parahippocampalcortex, and hippocampal formation. In a second experiment, authors studies the functional contributions of each component of the DMN. Participants were asked to answer multiple choices questions about self or non-self that were framed in the future or in the present. For example, future self questions asked about hypothetical autobiographical events that were to be experienced by the participant (e.g., “Think about where you will be and who you will be with tomorrow afternoon during lunch. Who will you be eating lunch with: no one, your significant other, or someone else?”). For the future non-self questions, participants were asked questions that required semantic knowledge about the future (e.g., “In two days, a sporting event will be televised by reporters in the southwest United States. Is the type of sport more likely to be: rodeo, baseball, or another type of sport?”) (Andrews-Hanna et al., 2010b). The dMPFC subsystem was engaged when participants made self-referential judgments about their present situation or mental states. Based also on previous findings (e.g., Frith and Frith, 2003; Gusnard et al., 2001; Ochsner et al., 2004), authors hypothesized that the dMPFC subsystem may support self-judgments and mental state inference of others. In contrast, the MTL subsystem was preferentially engaged during episodic judgments about the personal future. In general, those brain areas are fundamental for past and future autobiographical thinking, episodic memory, and contextual retrieval (Andrews-Hanna et al., 2014). These findings support the internal mentation hypothesis about the involvement of the DMN in the creating mental simulation. Several studies support the hypothesis that the DMN maintains spontaneous cognition (see 3.2; Binder et al., 1999; Mason et al., 2007; Christoff et al., 2009; Stawarczyk et al., 2011). Indeed, it was observed that while individuals mind-wander the DMN is active and it has previously been suggested that during mind wandering episodes individuals tend to escape from the here and now (see 3.1 and 3.2).

It is worth noting that many kinds of mental simulation show the common activation of the mPFC, that is part of the DMN (see 2.2 and 3.2). For example, a functional connectivity analysis (Spreng and Grady, 2010) revealed that activity of the mPFC was correlated with activity in other regions in the DMN during autobiographical memory, EFT, and theory of mind tasks. Moreover, several neuroimaging studies indicates that the mPFC, and in particular the vmPFC, is involved in EFT and episodic memory retrieval (Gilboa, 2004; Addis et al., 2007, 2009a; Summerfield et al., 2009; Bonnici et al., 2012), and also in constructing atemporal experiences (Hassabis et al., 2007a). In detail, there is evidence from neuroimaging studies that the ventral part of the medial prefrontal cortex is engaged while constructing complex scenarios (Hassabis and Maguire, 2007), supporting future affective simulations (Benoit et al., 2014), when thinking about the self in time (D'Argembeau et al., 2010b), and during mind wandering (Christoff et al., 2009; Andrews-Hanna et al., 2010a) (see also 1, 2.2 and 3.2). Together, these results lead to an interesting question: is activity in vmPFC necessary for different forms of deliberate and more automatic forms of mental simulation? This is the question we begin to answer with this thesis project.

5 Experiment 1 - Ventromedial prefrontal damage causes a pervasive impairment of episodic memory and future thinking

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5.1 Introduction

Human beings can imagine vividly episodes that happened to them in the past and episodes that may occur in their future, this capacity is called mental time travel (MTT; see chapter 2). MTT may have positive effects on wellbeing and decision-making. For example, future-oriented thought increases the overall level of happiness (Quoidbach et al., 2009), and reduces temporal discounting (TD), that is the tendency to devalue a reward as the delay until its delivery increases, which may result in preferences for smaller-immediate over larger-later rewards (Peters and Büchel, 2010; Benoit et al., 2011).

Remembering the past and imagining the future rely on a common "core" network of brain regions, including the vmPFC. As mentioned previously (see chapter 4), these brain regions also take part in the DMN, a network of brain regions particularly active when individuals tend to switch their attention inward, for example towards memories, desires, and plans for the future (see 2.1 and 2.2). Other evidence for the common neural bases of episodic memory and future thinking comes from cases of patients with brain damage (see 2.3). For instance, amnesic patients with MTLs damage or bilateral parietal lobe damage are as deficient in imagining novel experiences as they are in remembering past experiences (Tulving, 1985; Klein et al., 2002; Hassabis et al., 2007b; Berryhill et al., 2010; Race et al., 2011).

The structural overlap between remembering and imagining personal events can be interpreted in functional terms: as two instances of MTT, they may share MTT's component processes (see 2.1), such as "autonoetic consciousness" (Tulving, 1985; Wheeler et al., 1997), and "self-projection" (Buckner and Carroll, 2007). Remembering past and imagining future events, however, also commonly engage general constructive processes needed to access and recombine stored episodic details (Schacter et al., 2008, 2012) and generate the spatial context for these details to reside ("scene construction"; Hassabis and Maguire, 2007). These processes are necessary for MTT, but not specific to MTT, because any experience, whether self-relevant or not, and whether located in the past, the future, or atemporal, equally needs to be assembled and staged (whereas MTT refers specifically to mental *time* travel in *subjective* time; Wheeler et al., 1997).

Differences in brain activity between past and future MTT have also been noted, for example in frontopolar, dorsomedial, and ventrolateral prefrontal cortices, which were more active during construction of future compared to past events (Okuda et al., 2003; Addis et al., 2007; Benoit and Schacter, 2015). These differences have been generally related to the higher demands EFT (compared to remembering) places on constructive processes, requiring the flexible recombination and integration of details from multiple episodes into an event not experienced before (Schacter et al., 2012). A few reports have investigated the causal role of prefrontal cortex in episodic memory and future thinking (see also 2.3). Berryhill and colleagues (2010) demonstrated that patients with lesions to the lateral prefrontal cortex were impaired at imagining novel experiences, however they possess preserved autobiographical memory. Patients with Parkinson's disease show intact episodic remembering but impaired future thinking, with the degree of impairment related to executive functioning (de Vito et al., 2012).

Weiler and colleagues (2011) described patients with lesions in the medial dorsal thalamus, which is connected with prefrontal cortex, who could remember personal past experiences but had difficulties at imagining future episodes. Interestingly, patients' deficits were even more marked when they had to imagine events happening to other people. Moreover, patients with traumatic brain injury involving prefrontal cortex show deficits in both remembering the past and imagining the future (Rasmussen and Berntsen, 2014). Also, frontotemporal dementia causes a similar impairment in past and future MTT, although EFT and remembering deficits correlate with atrophy in frontopolar and medial prefrontal cortices, respectively (Irish et al., 2013). These findings suggest that prefrontal cortex is involved in MTT, but different regions of prefrontal cortex may mediate different processes of MTT.

In this experiment we focus on vmPFC. Many lines of research have suggested a possible involvement of vmPFC in future thinking (see 1, 2.3, and 4). Patients with lesion to vmPFC (vmPFC patients) show a short future time perspective (Fellows and Farah, 2005), they appear "myopic" to the future consequences of their choices (Bechara et al., 1994), and show steeper TD than healthy and brain-damaged controls (Sellitto et al., 2010). Moreover, vmPFC patients may exhibit a disorder of memory, named "confabulation", involving false recall and recognition of events that did not actually happen (Gilboa and Moscovitch, 2002; Gilboa et al., 2006), indicating that past MTT is also compromised.

The first aim of the present work is to investigate whether vmPFC is critically and equally involved in past and future MTT. A second aim of the study relates to the fact that MTT is strongly connected to the self and identity (Conway and Pleydell-Pearce, 2000), and that vmPFC is known to be strongly implicated in self-related processing (e.g., D'Argembeau, 2013). Considering that vmPFC is implicated in MTT and in self-related processing, we predicted that this region would be crucial to remember personal past events and imagine personal future ones, but not to conceive events happening to others. To test our hypotheses, we studied how vmPFC patients and healthy controls remember personal past events and imagine personal future events at different timeframes, and how they imagine events that may happen to a "close" other (family member) or a "distant" other (President of the Italian Republic).

5.2 Methods

5.2.1 Participants

Participants included 7 patients with vmPFC damage (vmPFC patients; 7 males, age: M = 44.1, SD = 12.6; years of education: M = 10.8, SD = 2.7) and 11 healthy individuals (11 males, age: M = 41.6, SD =11.9; years of education: M = 11.2, SD = 2.5), matched to patients in terms of age (t = - 0.43, p = 0.68), and education (t = 0.26, p = 0.80). Patients were recruited at the Centre for Studies and Research in Cognitive Neuroscience, Cesena, Italy. vmPFC patients' lesions were the results of the rupture of an aneurysm of the ACoA in 5 cases, and traumatic brain injury (TBI) in 2 cases. Lesions were bilateral in all cases, though often asymmetrically so (see Figure 1). Included patients were in the stable phase of recovery (at least 1 year post-morbid), 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 Ethical Committee of the Department of Psychology, University of Bologna.

5.2.2 Lesion analysis

Patients' individual lesions, as shown in the most recent magnetic resonance imaging (MRI; N = 3) or computerized tomography (CT; N = 4) images, were manually drawn by a neurologist (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 and Brett, 2000) (see also Karnath et al., 2004; Moro et al., 2008; Tsuchida and Fellows, 2012). This template is approximately oriented to match Talairach space (Talairach and Tournoux, 1988) and is distributed with MRIcro. The standard template provides various anatomical landmarks to help experts plot the size and localization of the lesion using structural features such as sulci and gyri as guides. 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). Manual segmentation/registration procedures have the limit to rely greatly on anatomical expertise, and to be subjective in nature. On the other hand, they circumvent problems frequently encountered by automated normalization procedures, such as (1) warping scans from individuals with brain injury, which may be affected by structural distortions related to the lesion and not easily compensated for (e.g., ventricular enlargement, large regions of atypical voxel intensity values, artifacts induced by the presence of metallic clips), and (2) combining subjects scanned with different imaging modalities (e.g., MRI vs. CT) (see Fiez et al., 2000; Kimberg et al., 2007). With respect to (1), when tracing lesions relative to scans with a surgical clip present in which artifacts made it difficult to observe damaged tissue, if damage was evident above and below the slices containing clip artifacts, then it was extrapolated that the lesion also included the region occupied by the clip (see also Ghosh et al., 2014). As for (2), when registering lesions documented in scans with slice thickness different from that of the standard template (1 mm), if damage was evident in two consecutive slices of the original image, then it was extrapolated that the lesion also included the region in between, and drawn on the corresponding slices of the template. MRIcro software was used to estimate lesion volumes (in cc) and to generate lesion overlap images.

Figure 1 shows the extent and overlap of brain lesions in vmPFC patients. Brodmann's areas (BA) affected in the vmPFC group were areas BA 10, BA 11, BA 24, BA 25, BA 32, BA 46, BA 47, with region of maximal overlap occurring in BA 11 (M = 19.70 cc, SD = 11.62, about 30% of BA 11’s volume), BA 10 (M = 14.20 cc, SD = 4.24, about 38% of BA 10’s volume), and BA 32 (M = 8.05 cc, SD = 2.98, about 25% of BA 32’s volume).

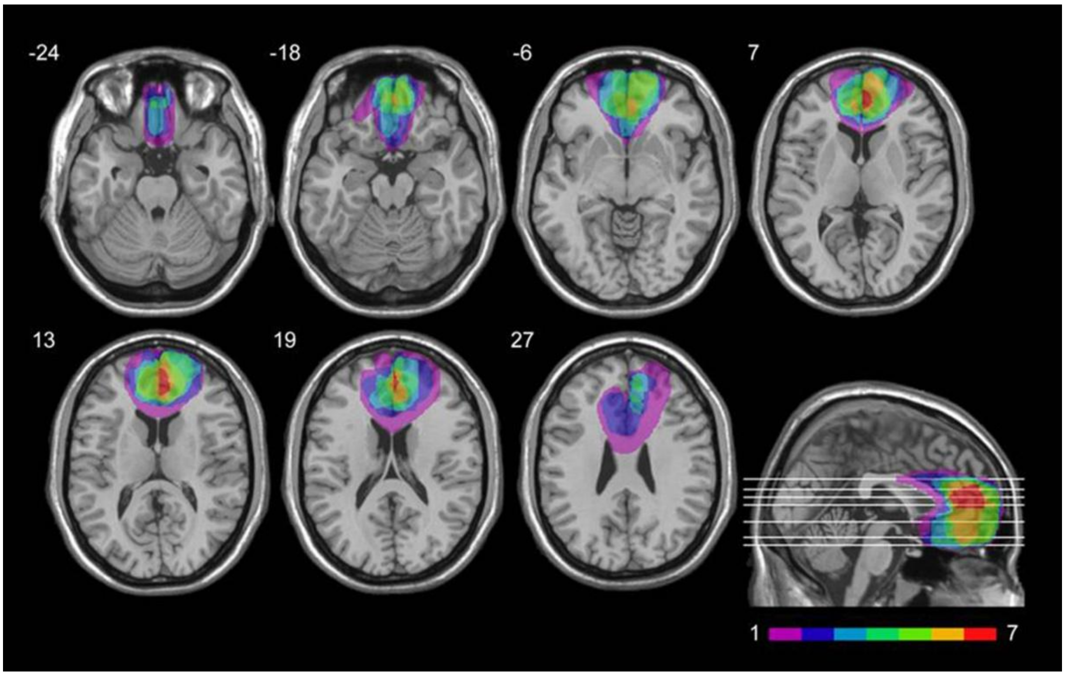

Figure 1. Extent and overlap of brain lesions. The figure represents vmPFC patients' lesions projected on the same seven axial slices and on the sagittal view of the standard Montreal Neurological Institute brain. The white horizontal lines on the sagittal view are the positions of the axial slices, and the white numbers belong to the axial views are the z-coordinates of each slice. The color bar indicates the number of overlapping lesions. Maximal overlap occurs in BA 11, 10, and 32. The left hemisphere is on the left side.

5.2.3 Neuropsychological assessment

A standardized neuropsychological assessment showed that vmPFC patients' general cognitive functioning was generally preserved, as indicated by the average scores obtained in the Mini Mental State Examination and the Raven Standard Matrices (see Table 1). Patients reported normal scores also in verbal and spatial short-term memory, as well as in working memory tests. Executive functions were generally preserved, with the exception of performance in the Wisconsin Card Sorting Test, suggesting a deficit in cognitive flexibility. We note that TBI patients evinced marginally lower semantic fluency (Mann-Whitney Z = 1.93, p = 0.09) and working-memory performance compared to ACoA patients (t = -2.53, p = 0.06, Crawford and Garthwaite, 2002). Long-term memory was weak. In the Buschke–Fuld Test (Buschke and Fuld, 1974), a standardized list learning task involving free recall, patients exhibited a highly pathological score (Spinnler and Tognoni, 1987), and performance in a prose-passage recall task was poor, although within the normal limits (Spinnler and Tognoni, 1987) (see Table 1). Patients did not show spontaneous confabulation, based on clinical evidence, their behavior in real life, and interviews with family members: patients did not confabulate without apparent prompting (Kopelman, 1987) or act upon erroneous memories (Schnider, 2008).

vmPFC patients (but not healthy controls) also completed a computerized TD task (Sellitto et al., 2010). In a series of trials, patients chose between an amount of (hypothetical) money that could be received immediately (e.g., 20 Euros) and another amount that could be received after a delay (40 Euros). Participants made five choices at six delays: 2 days, 2 weeks, 1 month, 3 months, 6 months, and 1 year. Using a staircase procedure, the amount of the immediate reward was adjusted based on the participant's choices, to estimate the rate at which the subjective value of a reward decays with time. This was assessed through two indices: the TD parameter k (Green and Myerson, 2004), 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 TD function, using a nonlinear leastsquares algorithm. The larger the value of k, the steeper TD, the more participants were inclined to choose small-immediate rewards over larger-delayed rewards. To calculate AUC, delays and subjective values were first normalized: 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 (Myerson et al., 2001). The AUC is the sum of the areas of all the trapezoids, and varies between 0 and 1. The smaller the AUC, the steeper TD.

5.2.4 Stimuli

Twenty four cue words (frequency: M = 65.04, SD = 105.55; imageability: M = 5.89, SD = 0.5; concreteness: M = 5.84, SD = 0.96; familiarity: M = 6.65, SD = 0.08), were selected from Burani et al. (2001), and allocated randomly to 4 lists of 6 words which did not differ significantly in frequency, imageability, concreteness, or familiarity (Kruskall-Wallis H < 1.96, p > 0.58 in all analyses). The assignment of the lists to the 4 experimental sessions (3 self-related, 1 other-related), the assignment of the different cue words within each list to different timeframes (see below), as well as the order of administration of the different time-frames, were determined randomly for each participant.

Table 1. vmPFC patients’ clinical information.

vmPFC patients:	P 1	P 2	**P 3**	**P 4**	P 5	P 6	P 7	Mean (ES)
SRM	35	33	**42**	**21**	47	42	34	36.3 (3.1)
MMSE	25	28	**28**	**21***	29	24	29	26.3
Verbal Judgments	44	54	**40**	**48**	45	58	52	48.7 (2.6)
Corsi test:								
Span	4	6	**5**	**3***	7	5	6	5.1 (2.7)
Supra span	26.6	28.5	**27.9**	**3.3***	28.7	16.9	27.8	22.8 (3)
DigitSpan	5	7	**6**	**7**	7	5	6	6.1 (3.7)
Working Memory:								
Misses	2	1	**7***	-	1	0	4*	2.5
False alarms	4*	8*	**0**	**-**	3	17*	0	5.3
Buschke-Fuld LTM	26 *	126	**82***	**67***	56*	35*	103	70.7 (0.6*)
Prose recall	13.5	13.8	**8**	**6.3**	7	3.3*	13.5	9.3 (1.6)
Tower of London test:								
Number of moves	46	44	**38**	**100***	31	22	44	46.4
WCST								
Perseverative errors	28	64 *	**37***	**-**	76 *	60*	32*	49.5
Stroop test:								
Errors	0	0	**0**	**0**	0.5	0	1	0.2
Verbal fluency:								
Phonemic	30	26	**25**	**23**	20	19	33	25.1(1.7)
Semantic	51	45	**35**	**30**	55	39	39	42(3)
TD rates:								
K	0.157	0.001	**0.1212**	**0.00005**	0.0164	0.007	0.0741	0.05
AUC	0.15	0.8	**0.29**	**0.98**	0.39	0.5	0.18	0.47

Note. Uncorrected scores. SRM = Standard Raven Matrices; MMSE = Mini Mental State Examination; LTM = long-term memory score; WCST = Wisconsin Card Sorting Test; TD = Temporal Discounting; k = temporal discounting parameter; AUC = area under the curve. Dashes indicate data not available. Asterisks indicate performance below the normal limits. Values in bold denote patients with Traumatic Brain Injury. In the last column, we report mean uncorrected scores, and, in brackets, mean Equivalent Score (ES), when available. The ES ranges from 0-4, with 0 = pathological performance, 1 = borderline performance, 2 – 4 = normal performance.

5.2.5 Episodic memory and future thinking task

We used an adaptation of the Crovitz task (Crovitz and Schiffman, 1974), comprising both a self-related condition (18 events administered in 3 separate sessions) and an other-related condition (6 events in 1 session). To prevent fatigue, participants received the 4 experimental sessions in 4 different days, at least 1 week apart.

5.2.5.1 Self-related condition

Participants remembered personal past events and imagined personal future events in as much detail as possible in response to cue words (Crovitz and Schiffman, 1974; Addis et al., 2007). All events had to be specific in time and place, and have lasted minutes or hours, but not more than a day. Future events had to be plausible, but novel. In each trial, the instructions specified (1) the type of task ("recall past event" or "imagine future event"), (2) the timeframe for past events ("yesterday", "last year", or "5 years ago") or future events ("tomorrow", "next year", or "in 5 years"), and (3) the cue word. Participants were told to use the cue-words flexibly: the event did not have to strictly involve the named object; participants could freely associate so that they would be successful in generating an event. Moreover, if a cue-word proved completely ineffective in eliciting any event, participants could choose another cue-word from an additional list of 24 cue words matched in frequency, familiarity, concreteness and imageability to the original cue-words ($p > 0.09$ in all cases).

Participants recounted the event they had in mind for 3 minutes (recall phase), then a probe appeared to encourage greater usage of details (i.e., "Do you want to add something?"), and participants could add detail to their descriptions for an additional minute. Participants then rated the events on a Likert scale ranging from 1-8 for (a) vividness (1, “not vivid”; 8, “extremely vivid”), (b) valence (1, “very negative”; 8, “very positive”), (c) current emotion (i.e., the emotion felt at the time of recalling/imagining the event: 1, “not intense”; 8, “extremely intense”), (d) past/future emotion (i.e., the emotion felt at the time of the past event/that would be felt if the future event occurred: 1, “not intense”; 8, “extremely intense”), (e) personal importance of the event (1, “not important ”; 8, “extremely important/life-changing”), (f) feeling of re/pre-experiencing (1, “not at all”; 8, “completely”), (g) temporal connectedness (i.e., the perceived similarity of the current self to the self in the past/future event: 1, “very different”; 8, “exactly the same”), and (h) visual perspective (field vs. observer perspective).

In each experimental session, participants remembered 3 events (happened “yesterday”, “last year”, and “5 years ago”) and imagined 3 future events (to happen “tomorrow”, “next year” or “in 5 years”), for a total of 18 events (9 past and 9 future events).

5.2.5.2 Other-related condition

Participants imagined future events that may occur in 1 year to a close other (a family member; 3 events) and a distant other (the President of the Italian Republic, who at the time of testing was Giorgio Napolitano; 3 events) using words as cues. All events in the close other condition had to pertain to the same family member, whom participants chose at the beginning of the session. Procedures in the other-related condition were similar to those in the self-related condition, with the exception that the cueing slide specified whether the subject had to imagine a future event happening to a “family member” or “Giorgio Napolitano”. Participants then rated the event across a number of different categories. Ratings from (a) to (e) were identical to those in the self-related condition. Participants also rated other-related events for (f) others’ emotions (i.e., the emotions the other would feel if the event happened: 1, “not intense”; 8, “extremely intense”), (g) others’ temporal connectedness (i.e., the similarity between the other’s current self and the other’s self during the future event, as perceived by the participant: 1, “very different”; 8, “exactly the same”), and (h) similarity to the self (i.e., the degree to which the participant feels similar to the close/distant other: 1, “very different”; 8, “exactly the same”).

5.2.6 Scoring

Testing sessions were recorded to enable transcription and later scoring of participants’ reports. Participants’ records were scored using the Autobiographical Interview protocol developed by Levine et al. (2002). Briefly, 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).

Two raters, blind to group membership and to the hypothesis of the study, scored the transcripts independently. A main rater scored all events, and a second rater scored 1/3 of self-related and 1/3 of other-related events. Inter-rater reliability for internal and external details between the two raters were assessed with intra-class correlation (McGraw et al., 1996), which indicated high agreement between the two scorers. Coefficients for internal and external detail of self-related events were 0.97 and 0.95, respectively, and 0.98 for both internal and external details of other-related events.

5.2.6.1 Self-referential processing scoring

As suggested by a referee, we also coded self-relevant past and future events for self-references and references to other people (as in Kurczek et al., 2015). The first author marked all references to people and groups of people in both the subject (e.g., *I* went to Chianti) and object position of a sentence (e.g., the waiter handed red wine to *me*). References coded as self-references included first person singular and first person plural pronouns and possessive cases (Italian equivalents of I, me, my, mine, we, us, our, ours, etc). References to others included third person singular and third person plural pronouns and possessive cases (Italian equivalents of he, him, she, her, you, yours, they, them, theirs, etc). Repetitions of self and other references contained in a false start (e.g, *I I* went to Chianti) were counted only once. One difference between Italian and English is that in Italian the verb's desinence identifies the subject even if the pronoun is not explicitly stated (e.g., both "io andai" and "andai" mean "I went"), and it is the context that specifies whether it is more appropriate to make the pronoun explicit or not. Thus, also verbs with no personal pronouns expressed counted as self/other references in our scoring. We calculated a self-reference index as: Self references / (Self references + Other references) as in Kurczek et al. (2015).

5.2.7 Confabulated details

We checked the truthfulness of all events produced by vmPFC patients asking a close relative to provide corroboration. Erroneous details in demanding memory tasks are formally considered a measure of provoked confabulation (Kopelman, 1987; Schnider et al., 1996), which is dissociable from spontaneous confabulation (Schnider, 2008). However, assessing provoked confabulation in vmPFC patients is important to qualify their memory abilities. Confabulations in the past/future were defined as internal or external details representing information incongruous with the autobiographical history/possible future actions of the patient (or the close and distant other) or with an incorrect time reference, e.g., recalling an alleged accident at the luna park, imagining a future trip with a car already sold (Dalla Barba et al., 1997; Moscovitch and Melo, 1997). We did not check the truthfulness of events produced by healthy controls.

5.2.8 Statistical analyses

For each event, internal and external details were tallied. Preliminary analyses indicated that the effect of general probe was very slight in comparison to free recall of both self-related and other-related events. Therefore, for clarity, we report the data collapsed across the free recall and general probe phases. For each condition, the details were averaged across the 3 events, separately for internal and external categories. The main analyses were conducted on patients' complete reports, including both veridical and confabulated details. Internal and external confabulatory details were separated from the non-confabulatory details for further analysis (see Confabulation sections). Statistical analyses on details were performed using analysis of variance (ANOVA). Given that subjective ratings, were, in most cases, non-normally distributed (Kolmogorov-Smirnov $d > 0.42$, $p < 0.05$), these were analyzed using non-parametric statistics. Between-group differences were assessed with Mann-Whitney U tests, and within-group differences were assessed using Friedman ANOVAs and Wilcoxon matched pairs tests. We report results significant at $p < 0.05$, two-tailed.

5.3 Results

5.3.1 Self-related condition

5.3.1.1 Details

vmPFC patients produced fewer personal past (7.7 vs. 9.0) and personal future events (8.6 vs. 9.0) than controls, though group differences were not significant (Mann-Whitney Test: $p = 0.15$ in both cases), likely due to ceiling effects in healthy controls. Patients and controls used a similar number of extra cue-words to construct past (0.38 vs. 0.21) and future events (0.32 vs. 0.10) ($p > 0.15$ in both cases).

Figure 2 shows that vmPFC patients provided fewer internal details for both past and future events than healthy controls, for all time-frames. In contrast, vmPFC patients and controls produced a similar number of external details across conditions (see Figure 3). A repeated-measure ANOVA on the number of details with Group (vmPFC patients, healthy controls), Time (past, future), Distance (1 day, 1 year, 5 years), and Detail (internal, external) as factors revealed significant main effects of Group ($F_{(1,16)} = 8.67$, $p = 0.009$), Time ($F_{(1,16)} = 16.81$, $p = 0.0008$), and Detail ($F_{(1,16)} = 22.34$, $p = 0.0002$), which were qualified by a significant Group x Time x Distance x Detail interaction ($F_{(2, 32)} = 4.48$, $p = 0.02$). We followed-up on the 4-way interaction running ANOVAs on internal and external details separately, with Group, Time, and Distance as factors.

The ANOVA on the number of internal details showed a main effect of Group ($F_{(1,16)} = 10.02$, $p = 0.006$): vmPFC patients produced fewer internal details compared to healthy controls (13.80 vs. 25.51). A main effect of Time also emerged ($F_{(1,16)} = 13.47$, $p = 0.002$): both groups provided more internal details for past compared to future events (23.03 vs. 18.88). The interaction Group X Time X Distance was marginally significant ($p = 0.08$). This interaction refers to the fact that patients appeared particularly impaired in recalling events happened 5 years ago, the most remote time period we probed (14.1 vs. 29.4; $p = 0.01$), in line with evidence of vmPFC's involvement in remote memory coding (Bonnici et al., 2012). Less significant group differences emerged for events happened 1 year ago (13.4 vs. 26.5; $p = 0.03$), and to occur in 5 years (11.1 vs. 23.6; $p = 0.03$) or 1 day (11.7 vs. 24.7; $p = 0.03$). The same ANOVA on the number of external details showed a main effect of Distance ($F_{(2,32)} = 4.40$, $p = 0.02$), such that both groups provided fewer external details while describing events 1 day apart than 1 year apart (9.60 vs. 11.93; $p = 0.04$) or 5 years apart (9.60 vs. 12.60; $p = 0.01$), while no significant difference was found between events 1 year and 5 years apart ($p = 0.54$). The same results were obtained removing TBI patients from the vmPFC sample[1], and removing an outlier (i.e., for the 1 year ago condition) from the healthy control sample.

5.3.1.1.1 Confabulation

A content analysis revealed that 5 vmPFC patients produced some confabulatory details in recalling past events, whereas only one patient confabulated while imagining future events. We attribute the higher propensity to confabulate for the past than for the future to the fact that imagining the future was less strict than remembering the past in terms of timeframe constraints: a past event either happened 1 year or 5 years ago, whereas the same future event may be plausible whether it happens in one year or in 5 years. Indeed, most confabulated details originated from attributing "true" memories to the wrong timeframe.

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[1] Given that our patient sample included 2 TBI patients, and that TBI patients may have different neuropsychological profiles than ACoA patients, we ran again the ANOVA excluding TBI patients from the sample, to make sure the results were not driven by these patients. We confirmed our results. There was significant Group x Time x Distance x Detail interaction ($F_{(2,28)} = 4.86$, $p = 0.01$). Separate ANOVAs on internal and external details revealed that vmPFC patients provided fewer internal details than healthy controls (12.6 vs. 25.5; $F_{(1,14)} = 8.88$, $p = 0.01$) but a similar number of external details (10.8 vs. 12; $F_{(1,14)} = 0.35$, $p = 0.56$). Additionally, we found no significant differences in the number of internal or external details between ACoA and TBI patients across conditions (Mann-Whitney Z > -

The number of confabulatory details was highly variable across patients. For past events (collapsing across time periods), the number of confabulated internal details per event ranged from 0 to 8.66 (mean = 3.53, corresponding to 25% of internal details, SD = 3.52), and the number of confabulated external details ranged from 0 to 8.33 (mean = 2.12, corresponding to 21% of external details, SD = 3.09). The patient with the highest proportion of confabulated details (90% of internal details and 79% of external details) was an ACoA patient who had suffered from spontaneous confabulation in the past. The only patient that confabulated about the future produced 6 confabulatory internal details and 4 external details (collapsing across time periods) (40% and 50% of his internal and external details, respectively). This was a TBI patient with no history of spontaneous confabulation. An ANOVA on the number of confabulated details with Detail, Time, and Distance as factors only evinced a marginally significant effect of Detail ($p = 0.066$), such that more internal than external details were confabulated.

Importantly, the presence of confabulation did not affect the results regarding group differences in episodic remembering and future thinking reported above. Indeed, we re-ran the ANOVA excluding confabulated details and obtained the same results: vmPFC patients provided fewer internal details than healthy controls at each time frame, whereas external details were as frequent as in healthy subjects.

In sum, these results show that vmPFC patients produced fewer internal details for both past and future events but a similar amount of external details than healthy controls, indicating an impairment in both remembering and imagining personal events.

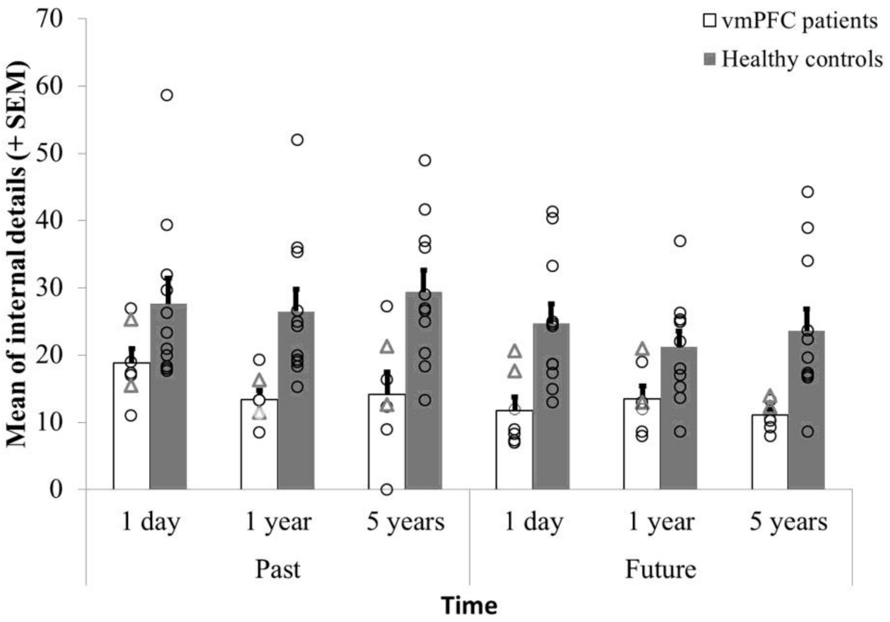

Figure 2. Mean number of internal details by group and timeframe in self-related condition. Error bars represent standard errors of the mean (SEM). Circles indicate performance of individual participants. Triangles denote TBI patients.

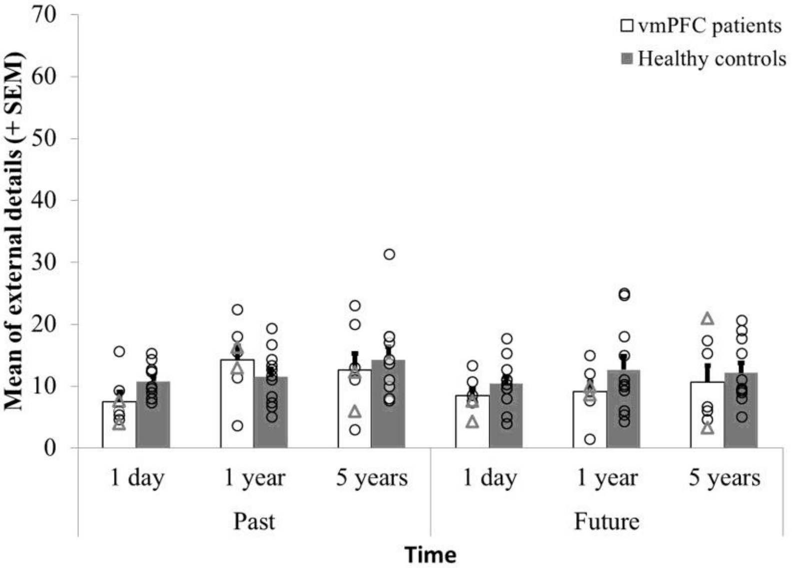

Figure 3. Mean number of external details by group and timeframe in self-related condition. Error bars represent the standard errors of the mean (SEM). Circles indicate performance of individual participants. Triangles denote TBI patients.

5.3.1.2 Self-referential processing

An ANOVA on the self-reference index with Group, Time, and Distance as factors yielded a significant Group X Time interaction ($F_{(1,16)} = 7.11$, $p = 0.02$): vmPFC patients evinced a higher self-reference index than healthy controls for past events (0.82 vs. 0.69, $p = 0.01$), and a normal self-reference index for future events (0.75 vs. 0.74; $p = 0.78$). Healthy controls tended to incorporate more self-references in future than in past events, whereas vmPFC patients showed the opposite tendency ($p = 0.07$ in both cases). The effect of Distance was marginally significant ($F_{(2,32)} = 2.92$, $p = 0.07$), such that participants tended to use more self-references during events distant 1 day than 5 years (0.78 vs. 0.72, $p = 0.03$).

Thus, at odds with Kurczek et al. (2015), vmPFC patients in the present study showed an *increased* tendency to use self-references, at least for past events. A possible interpretation of this finding is that vmPFC patients's self is mainly located in the past (as opposed to the future), consistent with their impaired future thinking (e.g., Sellitto et al., 2010). It is not clear, however, why this would not apply to vmPFC patients described in Kurczek et al. (2015). We propose another interpretation of inflated self-referencing in vmPFC patients, based on patients' autobiographical memory abilities. During autobiographical memory retrieval (as well as future thinking), individuals first access general autobiographical knowledge (e.g., lifetime periods/repeated events, such as "when I was in Toronto", "In the summer I always go to the beach"), and use it to probe specific events (Conway and Pleydell-Pearce, 2000; D'Argembeau and Mathy, 2011). Specific personal events may contain many characters (resulting in both self-references and other-references), but the higher order information used to access personal events is typically self-related (D'Argembeau and Mathy, 2011). We argue, therefore, that difficulties accessing specific events in our vmPFC patients (not present in Kurczek et al. (2015)'s patients) resulted in retrieval of more instances of autobiographical knowledge across repeated retrieval attempts, hence more self-references. That we observed increased self-referencing for past but not future events is consistent with the observation that events happened 5 years ago tended to be the most difficult to retrieve for vmPFC patients, and that provoked confabulation (commonly associated with effortful retrieval) was most pronounced for past events. If this interpretation is viable, then one should observe more semantic details in vmPFC patients than in healthy controls, at least for past events. Semantic details are the sub-category of External details under which personal semantic knowledge would be scored. Consistent with our hypothesis, an ANOVA on semantic details with Group, Time and Distance as factors evinced a significant Group x Time x Distance interaction ($F_{(2,32)} = 3.44$, $p = 0.04$): vmPFC patients provided more semantic details for past events occurred 5 years ago than healthy controls (7.52 vs. 4.61, $p = 0.04$). No other difference was significant ($p > 0.10$ in all cases).

5.3.1.3 Ratings

Subjective ratings were substantially similar between patients and controls. The only between-group difference emerged in the valence of past episodes happened 1 year ago ($z = -2.13$, $p = 0.03$), which were more positive in patients than in controls (6.38 vs. 5.50). Thus, the group differences in MTT previously discussed were unlikely to be due to differences in the events selected.

We also inspected potential differences in ratings within each group between past and future events and depending on time distance. There were a number of results worth noting (see Table 2 for the complete list of ratings and comparisons). Future events were rated as higher in personal importance than past events by vmPFC patients (4.85 vs. 3.76, $z = 2.03$, $p = 0.04$), and, though marginally, healthy controls (4.98 vs. 4.46, $z = 1.68$, $p = 0.09$). In both vmPFC patients and controls, events' importance improved with time distance, for both future events (vmPFC patients: $\chi^2 = 8$, $p = 0.02$; controls: $\chi^2 = 7.54$, $p = 0.02$), and, though less significantly, past events (vmPFC patients: $\chi^2 = 7.14$, $p = 0.03$; controls: $\chi^2 = 5.19$, $p = 0.07$). That is, both groups considered episodes to happen in 5 years more important than those to happen in 1 day (vmPFC patients: $z = 2.37$, $p = 0.02$; controls: $z = 2.66$, $p = 0.008$), and episodes occurred 5 years ago marginally more important than those happened 1 day ago (vmPFC patients: $z = 2.03$, $p = 0.04$; controls: $z = 1.68$, $p = 0.09$). Interestingly, in both vmPFC patients and healthy controls, temporal connectedness declined with time distance, for both future (vmPFC patients: $\chi^2 = 10.33$, $p = 0.006$; healthy controls: $\chi^2 = 15.95$, $p = 0.0003$) and past events (vmPFC patients: $\chi^2 = 9.65$, $p = 0.008$; healthy controls: $\chi^2 = 19.62$, $p = 0.00005$). Thus, both groups considered the current self as more similar to their self in events to occur in 1 day (vmPFC patients: $z = 2.20$, $p = 0.03$; healthy controls: $z = 2.76$, $p = 0.006$) or in 1 year (vmPFC patients: $z = 2.20$, $p = 0.03$; healthy controls: $z = 2.18$, $p = 0.03$) than in 5 years. The same pattern was found for past events: both groups judged their current self as more similar to their self in episodes occurred 1 day ago (vmPFC patients: $z = 2.20$, $p = 0.03$; healthy controls: $z = 2.93$, $p = 0.003$) or 1 year ago (vmPFC patients: $z = 1.99$, $p = 0.04$; healthy controls: $z = 2.93$, $p = 0.003$) than 5 years ago. Thus, in both vmPFC patients and healthy controls, events more distant in time tended to refer to more important experiences than events closer in time, and future/past selves were perceived as progressively more different from the current self with time. Despite the general absence of differences in past and future events' characteristics between groups, patients and controls differed in their ability to re-experience events. For healthy controls, the feeling of re-experiencing past events ($\chi^2 = 8.4$, p = 0.01) was modulated by time distance, such that events occurred 1 day ago were re-experienced more strongly than events occurred 5 years ago (z = 2.55, p = 0.01). No such modulation of re-experiencing was observed in vmPFC patients (p = 0.61).

Table 2. Mean ratings for self-related events by group and timeframe. Standard errors of the mean are in brackets.

		Past			**Future**		
		1 day	**1 year**	**5 years**	**1 day**	**1 year**	**5 years**
Vividness	HC	6.70(0.32)	6.47(0.39)	6.39(0.35)	6.65(0.29)	5.96(0.35)	6.21(0.29)
	vmPFC	5.90(0.43)	6.57(0.48)	5.43(0.75)	5.52(0.45)	5.74(0.56)	5.48(0.48)
Valence	HC	5.20(0.32)	5.50(0.25) ∧	5.12(0.50)	5.48(0.33) ϕ	4.88(0.52)	5.98(0.37)
	vmPFC	4.69(0.68)	6.38(0.31)	5.33(0.46)	5.88(0.31)	4.74(0.60)	6.72(0.40)
Current emotion	HC	5.21(0.51)	5.80(0.40)	5.88(0.44)	5.30(0.54)	5.26(0.48)	5.59(0.44)
	vmPFC	4.36(0.73)	5.57(0.68)	5.43(0.89)	5.38(0.31)	5.26(0.69)	5.33(0.38)
Past/future emotion	HC	5.82(0.42)	6.65(0.24)	6.36(0.40)	5.61(0.56) ϕ	6.35(0.35)	6.76(0.25)
	vmPFC	4.43(0.58) ϕ	6.07(0.38)	6.86(0.44)	6.02(0.56)	6.74(0.46)	6.29(0.42)
Importance	HC	3.97(0.37)	4.73(0.40)	4.68(0.53)	4.21(0.41) ϕ	5.05(0.45)	5.70(0.32)
	vmPFC	2.71(0.50) ϕ	3.90(0.45)	4.67(0.52)	4.26(0.48) ϕ	4.76(0.49)	5.52(0.54)
Feeling of re-/pre-experiencing	HC	6.50(0.38) ϕ	6.35(0.39)	5.83(0.46)	6.49(0.44)	5.91(0.42)	6.01(0.41)
	vmPFC	5.50(0.64)	6.24(0.80)	5.71(0.87)	6.09(0.66)	5.43(0.77)	5.71(0.79)
Temporal connectedness	HC	7.68(0.18) ϕ	6.95(0.19)	5.01(0.40)	7.82(0.18) ϕ	6.64(0.30)	5.89(0.32)
	vmPFC	7.88(0.08) ϕ	6.88(0.52)	4.95(0.59)	7.48(0.26)ϕ	6.79(0.29)	5.67(0.52)
Visual perspective	HC	1.36(0.21)	1.36(0.21)	1.30(0.21)	1.30(0.21)	1.36(0.24)	1.42(0.24)
	vmPFC	1.00	1.00	1.09(0.09)	1.09(0.09)	1.09(0.09)	1.10(0.10)

Note: HC = healthy controls; vmPFC = vmPFC patients. Statistical comparisons: ∧ = significant group difference; ϕ = significant difference among past (symbol in past columns) or future (symbol in future columns) timeframes.

5.3.2 Other-related condition

vmPFC patients produced fewer close other’s events (2.9 vs. 3) and distant other’s events (2.9 vs. 3) than healthy controls, though differences were not significant (all p values > 0.32), probably due to ceiling effects in controls. Patients and controls used a similar number of extra cue-words to construct close (0.4 vs. 0) and distant other’s events (0.1 vs. 0) (p > 0.32 in all cases).

5.3.2.1 Details

Figure 4, representing the mean number of internal and external details by participant group and character (self, close other, distant other), shows that vmPFC patients provided fewer internal details for all conditions compared to healthy controls, while they used a similar number of external details. We conducted an ANOVA on the number of details with Group, Character (self, close other, distant other), and Detail (internal, external) as factors. We included the data about imagining personal episodes to happen in 1 year (already analyzed above) in this ANOVA for comparison purposes. The ANOVA revealed a main effect of Group ($F_{(1,16)} = 5.52$, $p = 0.03$), and a main effect of Detail ($F_{(1,16)} = 11.23$, $p = 0.004$), which were qualified by a significant Group x Detail interaction ($F_{(1,16)} = 9.10$, $p = 0.008$). To follow-up on the interaction, we conducted separate ANOVAs on internal and external details. The ANOVA on internal details showed a main effect of Group ($F_{(1,16)} = 8.89$, $p = 0.009$): vmPFC patients produced fewer internal details compared to healthy controls (11.57 vs. 21.88).

The ANOVA on external details only showed a main effect of Character ($F_{(2,32)} = 4.48$, $p = 0.02$), such that the amount of external details was higher in the close compared to the distant other condition (13.83 vs. 8.80, $p = 0.003$). The same results were obtained removing TBI patients from the vmPFC sample.[2]

5.3.2.1.1 Confabulation

Confabulated details in future experiences of a close other were observed only in one patient (2 internal details and 2.66 external details, corresponding to 10% and 11% of internal and external details, respectively), the only patient who had confabulated during personal future events to happen in 1 year, where he had confabulated 9.66 internal details and 8 external details (74 and 80% of internal and external details, respectively). None confabulated about distant other events. Because of the overall paucity of confabulation for future events, we do not comment on the relative propensity to confabulate self-relevant vs. other-relevant events. Again, excluding confabulated details from the main analyses did not alter the results.

Thus, contrary to our hypotheses, these findings indicate that vmPFC also impairs episodic simulation of future events happening to others, suggesting that self-relevance is not critical to explain vmPFC's involvement in MTT. In fact, if we re-ran the primary ANOVA on data from the self-related condition with Group, Time, Distance and Detail as factors adding the number of internal and external details in the distant-other condition as covariates, the original effect of Group and the original 4-way interaction were no longer significant ($p > 0.19$ in both cases). This finding suggests that deficits in processes shared by the distant-other and the self-condition, such as core

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[2] We obtained the same results excluding TBI patients from the analysis. There was a significant Group x Detail interaction ($F_{(1,14)} = 9.83$, $p = 0.007$): separate ANOVAs on internal and external details showed that vmPFC patients provided fewer internal details than healthy controls (9.6 vs. 21.9, $F_{(1,14)} = 9.67$, $p = 0.008$), but a similar number of external details (10.7 vs. 11.5; $F_{(1,14)} = 0.11$, $p = 0.74$). Additionally, there were no significant differences in the number of internal or external details between ACoA and TBI patients across conditions (Mann-Whitney: $Z > -1.36$; $p > 0.19$ in both cases). We note that TBI patients tended to provide more internal details than ACoA patients for events happening to the close other (18.3 vs. 8.3, Mann-Whitney: $Z = -1.94$, $p = 0.09$).

constructive processes, may be sufficient to explain differences in MTT between vmPFC patients and controls.

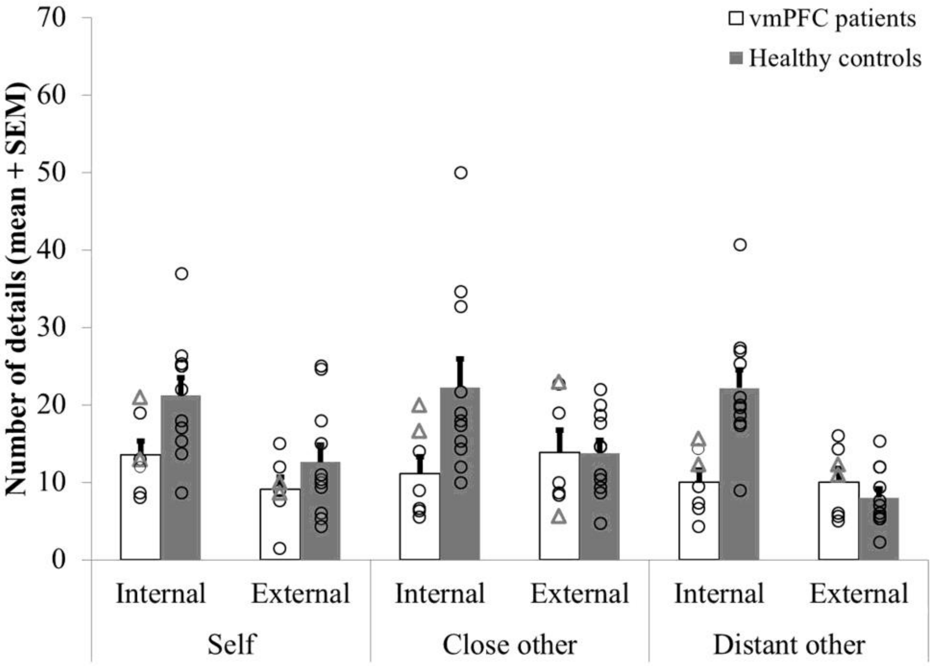

Figure 4. Mean number of internal and external details (for future events to occur in 1 year) by group and character. Error bars indicate standard errors of the mean (SEM). Circles indicate performance of individual participants. Triangles denote TBI patients.

5.3.2.2 Ratings

As for self-related events, subjective ratings for other-related events were substantially similar between groups. There were only a difference in valence, such that vmPFC patients rated distant other's events as less positive than healthy controls ($z = 2.52$, $p = 0.01$), and in close others' emotions, such that vmPFC patients considered the close other to be less emotionally affected by the event than did healthy controls ($z = 2.12$, $p = 0.03$).

We analyzed the differences in subjective ratings across different characters (self, close other, distant other). A number of results were worth noting (see Table 3 for the full set of ratings and comparisons). First of all, both vmPFC patients ($z = 2.20$, $p = 0.03$) and, though marginally, healthy controls ($z = 1.84$, $p = 0.07$) considered themselves as more similar to the close other than the distant other, suggesting that all participants complied with the instructions and differentiated between the close and distant other. Consistently, the emotions felt while imagining events were modulated by the character in both vmPFC patients ($\chi^2 = 9.09$, $p = 0.01$) and controls ($\chi^2 = 7.61$, $p = 0.02$): both groups reported more intense anticipated emotions for events happening to themselves (vmPFC patients: $z = 2.20$, $p = 0.03$; healthy controls: $z = 2.65$, $p = 0.008$), and, marginally, the close other (vmPFC patients: $z = 1.82$, $p = 0.07$; healthy controls: $z = 2.29$, $p = 0.02$) compared to the distant other. Events' vividness, too, was modulated by the character in vmPFC patients ($\chi^2 = 12$, $p = 0.002$), such that patients experienced personal episodes and episodes involving the close other as more vivid than those involving the distant other (self vs. distant other: $z = 2.37$, $p = 0.02$; close vs. distant other: $z = 2.37$, $p = 0.02$). Differences in vividness were not present in healthy controls ($p = 0.78$), likely due to ceiling effects (see Table 3).

Table 3. Mean ratings for other-related events to happen in 1 year by group and character. Self-related ratings are reported for comparison purposes.

		Distant other	Close other	Self
Vividness	HC	5.88(0.29)	6.03(0.32)	5.96(0.35)
	vmPFC	4.19(0.88) ϕ	5.10(0.79)	5.74(0.56)
Valence	HC	5.94(0.35) ∧	5.30(0.53)	4.88(0.52)
	vmPFC	4.41(0.45)	5.71(0.41)	4.74(0.60)
Current emotion	HC	4.57(0.64)	5.64(0.54)	5.26(0.48)
	vmPFC	3.67(0.78)	5.17(0.81)	5.26(0.69)
Future emotion	HC	4.54(0.63) ϕ	6.33(0.40)	6.35(0.36)
	vmPFC	3.98(0.97) ϕ	5.64(0.73)	6.74(0.46)
Importance	HC	5.24(0.47)	4.73(0.47)	5.05(0.45)
	vmPFC	4.24(0.46)	4.19(0.51)	4.76(0.49)
Temporal connectedness	HC	7.27(0.33) ϕ	7.30(0.23)	6.64(0.30)
	vmPFC	6.83(0.38)	6.07(0.62)	6.79(0.29)
Others' Emotions	HC	6.24(0.55) ϕ	7.15(0.36) ∧	-
	vmPFC	5.36(0.52)	5.83(0.63)	-
Personal connectedness	HC	3.18(0.55)	5.18(0.46)	-
	vmPFC	2.57(0.95) ϕ	5.43(0.73)	-

Note: HC = healthy controls; vmPFC = vmPFC patients. Statistical comparisons: ∧ = significant group difference; ϕ = significant differences among characters. Standard errors of the mean are in brackets.

5.3.3 MTT and TD: exploratory analyses

Given that TD behavior has been related to EFT in healthy individuals (Peters and Büchel, 2010), we investigated the relation of TD and MTT in vmPFC patients. Would patients with the stronger abilities to imagine future events be also those that discount the future less steeply? To test this hypothesis, we assessed the correlation between TD measures and an index of the tendency to access self-related future events episodically, calculated as (Future internal details/Future external details)/(Past internal details/Past external details). We controlled for episodic remembering to obtain a relatively pure index of patients' ability to project themselves into the future, as opposed to an index of the efficiency of the episodic memory system in general. This "future episodicity index" reflects patients' tendency to access the future episodically, taking into account their overall episodic memory abilities. It is worth noting that the future episodicity index was not different between vmPFC patients and controls (t = -0.40, p = 0.70), consistent with the fact that patients were equally impaired in episodic remembering and future thinking. The future episodicity index correlated significantly with both AUC (r = 0.82, p = 0.02) and *k* (r = -0.78, p = 0.03, *two-tailed*): the more vividly patients imagined personal future events, the more inclined they were to choose large future rewards over smaller-immediate rewards, meaning less steep TD. We note that no correlation emerged between AUC or *k* and the (future) internal/external details ratio for other-related events (collapsing across the close and distant other conditions) (p > 0.53 in both cases).

5.3.4. MTT and vmPFC: exploratory analyses

We investigated whether MTT abilities correlated with lesion volume in vmPFC. Brain lesions of vmPFC patients overlapped maximally in BAs 32, 11, and 10. By using partial correlation analyses, we investigated whether the number of internal and external details (collapsed across past and future self-related conditions), and the future episodicity index correlated with lesion volume in each of the three BAs, partialing out the effect of lesion volume in the other two BAs. We found that lesion volume in BA 32 correlated significantly (r = -0.93; p = 0.02, *two-tailed*) and lesion volume in BA 11 correlated marginally (r = - 0.88, p = 0.05, *two-tailed*) with the future episodicity index, such that patients with bigger lesions were relatively less inclined to imagine the future as rich in episodic detail. In contrast, we did not find any significant correlation between lesion volume and the number of internal or external details (all p values > 0.27, *two-tailed*). As well, lesion volume was not related to the number of internal detail, external details, or to the internal/external details ratio relative to other-related events (collapsing across the close and distant other condition) (p > 0.59 in all cases).

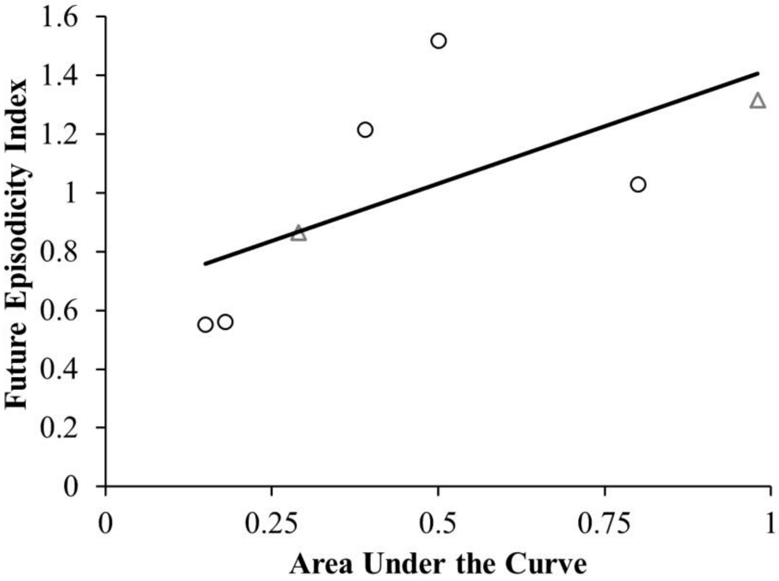

Figure 5. Scatterplot of the correlation between the Area under the curve (AUC) in the temporal discounting (TD) task and the Future episodicity index in vmPFC patients. Triangles denote TBI patients.

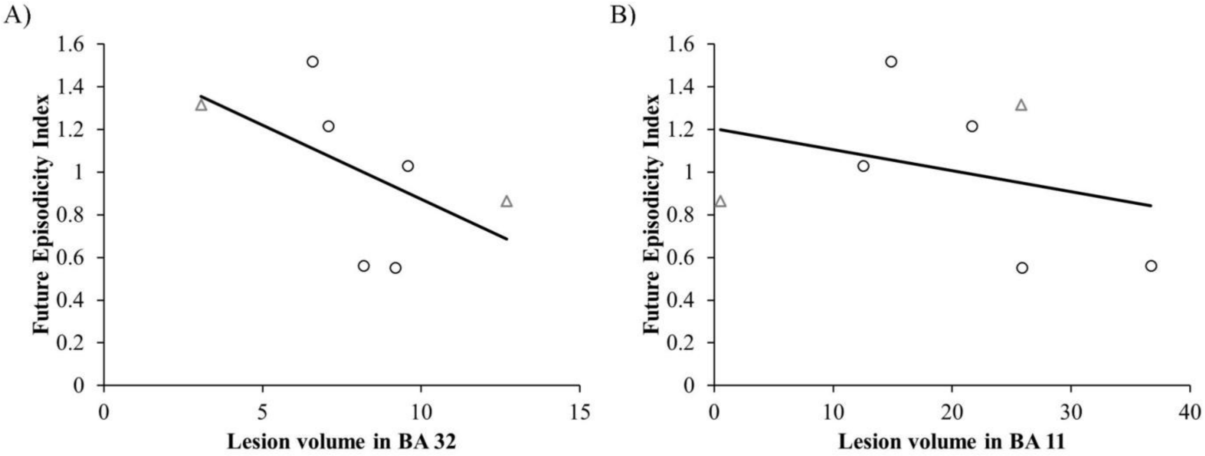

Figure 6. Scatterplot of the correlation between lesion volume in BA 32 (panel A) and in BA 11 (panel B) and the Future episodicity index. Triangles denote TBI patients.

5.4 Discussion

This study investigated the involvement of vmPFC in remembering personal past events and imagining personal future events, as well as in imagining future experiences of close and distant others. We found that vmPFC patients are impaired in remembering personal past events, and the same difficulty appears for future events, and at any timeframe, indicating a pervasive impairment of MTT. For both past and future events, vmPFC patients provided fewer internal (episodic) details than healthy controls but a similar number of external details, indicating a selective impairment of the episodic memory system. vmPFC patients also produced confabulatory details, especially while remembering past events. These consisted mainly of fragments of true memories misattributed to the wrong timeframe, which is reminiscent of confabulating patients' problems at suppressing currently irrelevant memory traces (Schnider, 2008; see also Ciaramelli and Ghetti, 2007), and tendency to "recast" habits/repeated events as specific events (Serra et al., 2014). Interestingly, vmPFC patients' objective deficit in producing episodic details was accompanied by an irregular subjective experience of remembering (see also Ciaramelli and Ghetti, 2007), in that events that had occurred one day vs. 5 years prior did not differ in terms of the feeling of re-experiencing they engendered.

Previous research had shown results in line with ours. Moscovitch and Melo (1997) found impoverished descriptions of personal past (as well as historical) events in patients with presumed damage or dysfunction of the vmPFC using the Crovitz task (see also Ghosh et al., 2014). Levine (2004) showed that patients with ventral prefrontal damage produce fewer internal details but a similar number of external details than healthy controls during autobiographic memory retrieval, "presumably reflecting a state of consciousness partially stripped of the benefits of MTT and relatively constrained to the here and now" (Levine, 2004, p. 61). Our findings indicate that vmPFC damage precludes both past and future MTT, adding to previous evidence that deficits in episodic memory can be associated with specular difficulties in imagining future experiences (reviewed in Schacter et al., 2012). Contrary to our hypotheses, however, damage to vmPFC also reduced internal details during simulation of others' experiences, suggesting that vmPFC is crucial for event construction even when self-related processing is not.

Before discussing our results further, it is worth noting that these are unlikely to be due to blatant problems, on the vmPFC patients' part, with the representation of time or self, with the hypotheticality inherent to MTT, or with task instructions. In fact, several findings regarding event detail and phenomenology were remarkably similar between vmPFC patients and controls, and need be emphasized. First, all participants produced more internal details for past than for future events (see also Addis et al., 2008; D'Argembeau and Van der Linden, 2004), consistent with the fact that real events typically contain more detail than imagined events (Johnson et al., 1988). Across groups, personal importance was greater for future events, which are relevant to the achievement of one's goals, than for past events (D'Argembeau and Van der Linden, 2004; Addis et al., 2008). Moreover, both groups rated events distant in time as more personally important than events close in time. Possibly, whereas everyday events come to mind easily while looking for events close in time, constructing distant events requires more intense framing of memory search, for example based on goals characterizing lifetime periods (e.g., "when I was a PhD student…"), leading to the retrieval of relatively meaningful events (Conway and Pleydell-Pearce, 2000; D'Argembeau and Mathy, 2011). That vmPFC patients showed these normal modulations of events' features with time strongly suggests they did attempt MTT, and did so towards specific points of subjective time (as opposed, for example, to merely recast past memories as future events).

As well, several areas of preserved self-related processing need be noted. vmPFC patients, as well as controls, were aware that their current self was likely more similar to their self in one year than in five years, and their temporal connectedness was not different from the controls'. As well, patients felt more similar to the close than to the distant other, and reported more intense emotions and more vividness for self-related compared to other-related events. Again, this set of findings suggest that vmPFC patients differentiated between themselves, close others, and distant others, and could reflect on hypothetical selves.

Having established that vmPFC patients were able to differentiate between the self and others, and that they attempted MTT towards specific points in time, it remains to be explained why they could not construct specific events. This was unlikely to be due to a general problem in detail generation: vmPFC patients produced a normal number of external details. Moreover, verbal fluency measures were within the normal range in vmPFC patients. Additionally, vmPFC patients show normal discourse cohesion and coherence (Kurczek and Duff, (2012), and were found normally able to recount fairy tales and bible stories (Gilboa et al., 2006), which suggests preserved narrative abilities. Turning to more specific accounts, the fact that patients had difficulties with both self-related and other-related events suggests that self-related processing is not the primary factor driving vmPFC's involvement in MTT. That is, vmPFC patients' deficit does not seem one of "self"- projection (Buckner and Carroll, 2007), as it is apparent also when there is no explicit request for the *self* to be projected in a different time/place/perspective. One could argue that participants may still project themselves in the perspective of the protagonist while simulating others' event. This, however, should happen more while simulating events happening to close than to distant others (Rabin and Rosenbaum, 2012), yet vmPFC patients' performance was not modulated by others' closeness. Thus, we are not inclined to qualify vmPFC patients' deficit as one of self-projection.

We propose that vmPFC is needed to conceive any complex experience that is decoupled from the current perceptual environment. Imagining any event, including personal past and future events, as well as events in which we are not involved, requires retrieval of episodic details and semantic information to be assembled ("episodic simulation"; Schacter et al., 2012, 2008) and staged in a spatial context ("scene construction"; Hassabis and Maguire, 2007). vmPFC has long been implicated in strategic retrieval processes needed to constrain memory search, and monitor the appropriateness of recovered memories (Moscovitch and Melo, 1997; Gilboa et al., 2006). vmPFC might work in concert with the MTLs during event (re)construction, searching and monitoring episodic and semantic memories to be edited for recall, or combined flexibly to picture novel events. vmPFC, indeed, supports the integration of individual episodes' elements into common representations (Benoit, Szpunar, & Schacter, 2014; see also Zeithamova et al., 2012). Of course, construction of self-relevant vs. other-relevant events would require different proportions of episodic (autobiographical) and semantic memories. Both activities, however, demand retrieval and integration of individual details, and the construction of a coherent scene. Recently, we have found that damage to vmPFC impairs imagination of both future and fictitious, atemporal experiences (Bertossi et al., 2016a), which reinforces our view of vmPFC as involved in core constructive processes needed to simulate any complex event, whether located in time or not, self-relevant or not. Interestingly, patients with lesions in the occipital cortex were able to construct novel experiences (Bertossi et al., 2016a), suggesting that impaired event construction in vmPFC patients is not merely the effect of brain damage on performance in an effortful task, but rather the effect of damage inflicted on a well-delineated system for event construction (Hassabis and Maguire, 2007; Schacter et al., 2012), of which vmPFC and the MTLs are crucial, interconnected nodes (Andrews-Hanna et al., 2010b).

Further studies are needed to specify the nature of the contribution of vmPFC and the MTLs to event construction. vmPFC is critical for appropriate processing of schema-related information (Burgess and Shallice, 1996; Ghosh et al., 2014). During scene construction, this region may help activate/maintain stable schematic representations of relevant events (e.g., the typical day at the beach) around which to construct a specific event, for example by pointing to related, context-relevant past experiences to use as source of details (Preston and Eichenbaum, 2013). A failure in activating/maintaining schema-related knowledge may explain the production of events poor of episodic quality in vmPFC patients. We note that vmPFC patients did not generally endorse schema-irrelevant details (see also Bertossi et al., 2016). Even when confabulating, they recounted very typical experiences (dinners with friends, days at the park, etc.), though with few details, some of which misplaced in time. One patient stated that the day after he would have pruned all the trees of his garden. This was inconsistent with the fact that at the moment he could not move his hand properly. Whether this reflects impaired monitoring of details based on self-schema, or the attribution of a past memory (he used to pruned his trees) to the wrong timeframe, is not clear. In this work, we asked participants to imagine (but not remember) events happening to others. A more systematic investigation of both retrieval and imagination of self- and other-related events may help highlight the relation between confabulation and schema-related processing: because the self-schema is a particularly robust cognitive schema (Craik et al., 1999), a deficit in processing schema-related information should have a greater impact on the construction of self-related compared to other-related events. The status of confabulation may also be relevant. We tested vmPFC patients without spontaneous confabulation. It is possible, however, that vmPFC patients with spontaneous confabulation would provide experiences that would deviate from schema-related knowledge (Ghosh et al., 2014; Gilboa et al., 2006), and be implausible (see Cole et al., 2014).

EFT is one device (among many) humans use to escape the here and now (Boyer, 2008; Ciaramelli and di Pellegrino, 2011). The vivid simulation of future experiences (e.g., submitting a paper) may help resist the saliency of immediate rewards (e.g., listening to music all day), contrasting TD (Peters and Büchel, 2010; Benoit et al., 2011). In a previous study, we have shown that vmPFC patients have steep TD (Sellitto et al., 2010, including 3 of the patients described here). Although gathered from a relatively small group of patients, correlation analyses in the present study showed that the more impaired vmPFC patients were at imagining personal future events vividly, the steeper TD was, suggesting a relation between TD behavior and mnemonic processes mediated by vmPFC. Interestingly, both future MTT in this study and TD in Sellitto et al. (2010) correlated with lesion volume in BA 11 and BA 32, two crucial nodes of the core network (Benoit and Schacter, 2015). One possibility is that these two regions mediate processes implicated in future thinking selectively. Benoit and Schacter (2015), however, have shown that BA 10 is the vmPFC sub-region preferentially associated with EFT. Moreover, in a previous work we have found that lesion volume in BA 11 predicted imagination of future and fictitious experiences as well (Bertossi et al., 2016a). Another possibility, which we favor, is that BA 11 and BA 32, as part of the core network, mediate constructive processes needed for both past and future MTT (Benoit and Schacter, 2015), but are especially sensitive to experimental conditions that load maximally on those processes (e.g., future thinking). Indeed, even though we have highlighted a possible link between impaired future MTT and steep TD, we expect that, based on their pervasive event construction impairment, vmPFC patients would be equally impaired in mental operations requiring simulation of the past, for example counterfactual thinking (Gomez Beldarrain et al., 2005; De Brigard et al., 2013). vmPFC patients have impaired regret during decision-making (Camille et al., 2004), which supports this speculation.

One further aspect of the results needs consideration before concluding. A recent report has shown preserved self-projection but reduced self-referencing in vmPFC compared to controls (Kurczek et al., 2015), while we are showing impaired self-projection with increased self-referencing (for past events). Two key differences between the studies may help interpret this important discrepancy. First, we looked at free recall of “entire” events (i.e., lasting minutes or hours, not more than a day; in line with e.g., Addis et al., 2008, 2007; de Vito et al., 2012; Race et al., 2011), whereas participants in Kurczek et al. (2015) were guided to focus on circumscribed “fragments” of already selected events, and the analyses were restricted to those specific fragments. The two procedures, therefore, placed different demands on (and scored differently) the event *construction* phase. Second, vmPFC patients in the present study exhibited impaired declarative memory (e.g., on the Buschke-Fuld list learning task), whereas vmPFC patients tested by Kurczek et al. (2015) had relatively intact declarative memory. vmPFC, therefore, may be crucial to assemble complex (extended) events, probably mediating episodic memory processes (e.g., search, binding) that also operate during more traditional episodic memory tasks, such as list learning (see also Maguire and Mullally, 2013). The nature of the task and the degree of patients' episodic memory impairment may also, at least in part, explain the divergent findings on self-referencing. vmPFC patients in the present study had difficulties accessing specific personal episodes. This resulted in the retrieval of relatively more instances of higher order autobiographical memory structures (e.g., personal semantic knowledge) during event construction, which was apparent for past events. While specific episodes may involve many characters (resulting in both self- and other-references), personal semantic knowledge is typically self-referenced. A difficulty in accessing specific events, therefore, may translate in inflated self-referencing scores. Clearly, this is not expected if patients are normally able to access specific events, or if the task (or the scoring method) places less weight on the event *construction* phase, as we think is the case in Kurczek et al. (2015).

To conclude, we have shown that MTT is heavily impaired vmPFC patients, indicating that vmPFC is a crucial neural substrate of MTT, consistent with fMRI evidence. Given that vmPFC patients' impairment extended to the imagination of events happening to others, we propose that vmPFC is crucial for the construction of complex events alternative to the current reality, which enables simulation of both self-relevant and other-relevant events. This deficit constrains vmPFC patients into the present moment, with an abstract representation of their past and future but no possibility to re-experience or pre-experience specific events. The correlation between MTT abilities and TD, however, suggests that training patients to construct and experience specific future events may improve their future-based decisions.

6 Experiment 2 - Stuck in the here and now: construction of fictitious and future experiences following ventromedial prefrontal damage

[This study has been published in Bertossi E., Aleo F., Braghittoni D., Ciaramelli E., *Neuropsychologia*, 2016]

6.1 Introduction

It is typical of the human mind to detach occasionally from the present to imagine alternative scenarios, including future events (e.g., job interview in two days), past events (e.g., graduation two years ago), or merely fictitious experiences (e.g., being on the beach, not at work). Most frequently, such imaginative acts are future-focused, and goal-oriented (Smallwood et al., 2009; D'Argembeau et al., 2011).

There is much interest, therefore, in revealing the cognitive and neural bases of EFT. fMRI studies have shown that EFT engages regions that are also activated by episodic memory (see 2.1 and 2.2), including medial prefrontal and posterior cingulate cortex, frontal pole, angular gyrus, and MTLs (Okuda et al., 2003; Addis et al., 2007; Szpunar et al., 2007). The functional significance of this overlap has been related to component processes that EFT shares with episodic remembering, including processes specifically related to MTT, such as "autonoetic consciousness" (Wheeler et al., 1997), as well as constructive processes needed to simulate any event, whether or not located in subjective time, such as the ability to generate and visualize coherent spatial contexts ("scene construction"; Hassabis et al., 2007b), and to recover and integrate the distinct elements constituting the event (Schacter et al., 2008) (see 2.1). In the previous experiment we have shown that MTT is heavily impaired in vmPFC patients, indicating that vmPFC is a crucial neural substrate of MTT, consistent with fMRI evidence. Given that vmPFC patients' impairment extended to the imagination of events happening to others, we propose that vmPFC is crucial for the construction of complex events alternative to the current reality, which enables simulation of both self-relevant and other-relevant events. To test whether vmPFC is crucial for EFT, and contribute to elucidate its mechanistic role in EFT, we studied how patients with focal lesion to vmPFC, control patients with lesions outside the vmPFC (mainly occipital), and healthy individuals imagine future and fictitious experiences.

6.2 Methods

6.2.1 Participants

Participants included 16 patients with brain damage and 12 healthy individuals (see Table 4 for demographic information). Patients were recruited at the Centre for Studies and Research in Cognitive Neuroscience, Cesena, Italy. Patients were selected on the basis of the location of their lesion evident on MRI or CT scans.

Seven patients had lesions involving the vmPFC (vmPFC patients; see Table 4 for demographic information). Lesions were the results of the rupture of an aneurysm of the ACoA in 6 cases, and traumatic brain injury in 1 case. Lesions were bilateral in all cases, though often asymmetrically so (see Figure 7). Nine patients were selected on the basis of having damage that did not involve the vmPFC (control patients). In this group, lesions were unilateral in 7 cases (in the left hemisphere in 3 cases, and in the right hemisphere in 4 cases), and bilateral in 2 cases, and were all caused by ischemic or hemorrhagic stroke. Lesion sites mainly included the occipital cortex and the occipitotemporal area, and extended into the posterior lateral aspect of the temporal lobe (4 cases), the lateral frontal (1 case) and parietal cortex (1 case), and the cerebellum (2 cases). Included patients were in the stable phase of recovery (at least 3 months post-morbid), 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). There was no significant difference in lesion volume between vmPFC patients and non-FC patients (53 vs. 35 cc, Mann-Whitney $Z = 1.22$, $p = 0.25$). The healthy control group comprised 12 individuals matched to the patients on mean age, education, and gender. 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, 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.

6.2.1.1 Neuropsychological profile

Patients' general cognitive functioning was generally preserved, as indicated by the scores they obtained in the Raven Standard Matrices (RMS), the phonemic fluency test (PF), and the digit span test (DS), which were within the normal range in all cases, and similar between the patient groups (Mann-Whitney $Z > -0.17$, $p > 0.86$ in all cases) (see Table 4). vmPFC patients also received a more extensive neuropsychological evaluation aimed at qualifying their cognitive profile further. vmPFC patients reported normal scores in verbal short-term memory (Mean equivalent score (ES) = 3.86. Note that the equivalent score ranges from 0 = impaired performance, and 1 = borderline performance, to 2 - 4 indicating normal performance) (Spinnler and Tognoni, 1987), spatial short-term memory (ES = 2.86) (assessed with Digit Span and Corsi test, respectively), and working memory, assessed with the 2-back task from the Test Battery for Attentional performance (TEA) (T-score = 41, cut-off = 30) (Zoccolotti et al., 1994; Zimmermann and Fimm, 2002). Patients also exhibited normal performance in several tests tapping executive functions, such as the Tower of London test (T-score = 42) (Culbertson and Zillmer, 2000), phonemic (ES = 1.71) and semantic fluency (ES = 3.57), and the Stroop test (mean number of errors = 1.64, cut off > 7.5) (Spinnler and Tognoni, 1987). vmPFC patients, however, showed a borderline performance in the Wisconsin Card Sorting Test, which was characterized by many perseverative responses (T = 30), suggesting a deficit in cognitive flexibility. Long-term memory was weak: In the Buschke–Fuld Test (Buschke and Fuld, 1974), that is a standardized selective-reminding list learning task involving free recall, patients exhibited a highly pathological Consistent Long Term Retrieval score (ES = 0) (Spinnler and Tognoni, 1987). Performance in a prose-passage recall task was weak but within the normal limits (ES = 1.71) (Spinnler and Tognoni, 1987).

vmPFC patients did not show spontaneous confabulation, as indicated by clinical evidence and interviews with family members: patients did not confabulate without apparent prompting (Kopelman, 1987) or act upon erroneous memories (Schnider, 2008). However, their autobiographical memory was poor. Recently, we have tested episodic remembering and future thinking formally in a group of 7 vmPFC patients (see Experiment 1; including 4 of the patients tested here) using a modified Crovitz procedure (Crovitz and Schiffman, 1974; Bertossi et al., 2016b). Using words as cues, vmPFC patients and healthy controls remembered personal past events and imagined personal future events at different time frames (events happened 5 years/1 year/1 day ago and events that may happen in 1 day/1 year/5 years), and also imagined future events that may happen (in 1 year) to a close or distant other. Consistent with fMRI evidence (e.g., Addis et al., 2007), patients produced fewer internal details but a similar number of external details for both past and future events. vmPFC patients were impaired across all temporal conditions, but recall of events happened 5 years ago tended to be the most impaired, in line with vmPFC's involvement in remote memory coding (Bonnici et al., 2012). Despite the absence of spontaneous confabulation, patients produced erroneous details in the Crovitz procedure (on average, 15% of all the details produced). These details were incongruous with the autobiographical history/possible future actions of the patient or had an incorrect time reference, e.g., recalling an alleged accident at the amusement park, imagining a future trip with a car already sold (Dalla Barba et al., 1997; Moscovitch and Melo, 1997). Erroneous details in demanding memory tasks are formally considered a measure of provoked confabulation (Kopelman, 1987; Schnider et al., 1996), which is dissociable from spontaneous confabulation (Schnider, 2008). We observed erroneous memory details mainly during recall of past events, and rarely during imagination of future events, likely due to the fact that imagining the future was less strict than remembering the past in terms of timeframe constraints: a past event either happened 1 year or 5 years ago, whereas the same future event may be plausible whether it happens in one year or in 5 years. Importantly, eliminating erroneous details from patients' reports did not alter our main finding of a comparable impairment in episodic remembering and future thinking in vmPFC patients (Bertossi et al., 2016b).

Table 4. Participants' demographic and clinical information

Group	N	Age (Years)	Education (Years)	Sex	SRM	PF	DS
vmPFC patients	7	50.43(2.63)	12.14(1.30)	7 M	35.86(2.86)	26(1.71)	6.14(3.86)
Control patients	9	53.89(4)	11.89(1.39)	9 M	34.14(3.14)	34(2.75)	6.12(3.75)
HC	12	51.17(2.98)	11.50(0.84)	12 M	-	-	-

Note. vmPFC = ventromedial prefrontal cortex; HC = healthy controls; M = male; SRM = Standard Raven Matrices; PF = phonemic fluency; DS = digit span. For SRM, PF, and DS, we report the mean uncorrected scores and, in brackets, the mean equivalent score (with 0 = pathological performance, 1 = borderline performance, 2 – 4 = normal performance). For age and education, the values in brackets are standard errors of the mean.

6.2.2 Lesion analysis

For each patient, lesion extent and location was documented using the most recent clinical computerized tomography (CT; N = 4 vmPFC patients, 2 control patients) or magnetic resonance imaging (MRI; N = 3 vmPFC patients, 7 control patients). Lesions were traced by a neurologist with experience in image analysis directly on the T1-weighted template MRI scan from the Montreal Neurological Institute provided with the MRIcro software (Rorden and Brett, 2000; available at http://www.mricro.com/mricro). This scan is normalized to Talairach space. Superimposing each patient's lesion onto the standard brain allowed us to estimate the total brain lesion volume (in cc). Figure 7 shows the extent and overlap of brain lesions in vmPFC patients. Brodmann's areas (BA) affected in the vmPFC group were areas BA 10, BA 11, BA 24, BA 25, BA 32 (subgenual portion), and BA 47, with region of maximal overlap occurring in BA 11 (M = 23.56 cc, SD = 13.90), BA 10 (M = 13.38 cc, SD = 8.37), and BA 32 (M = 7.06 cc, SD = 3.34).

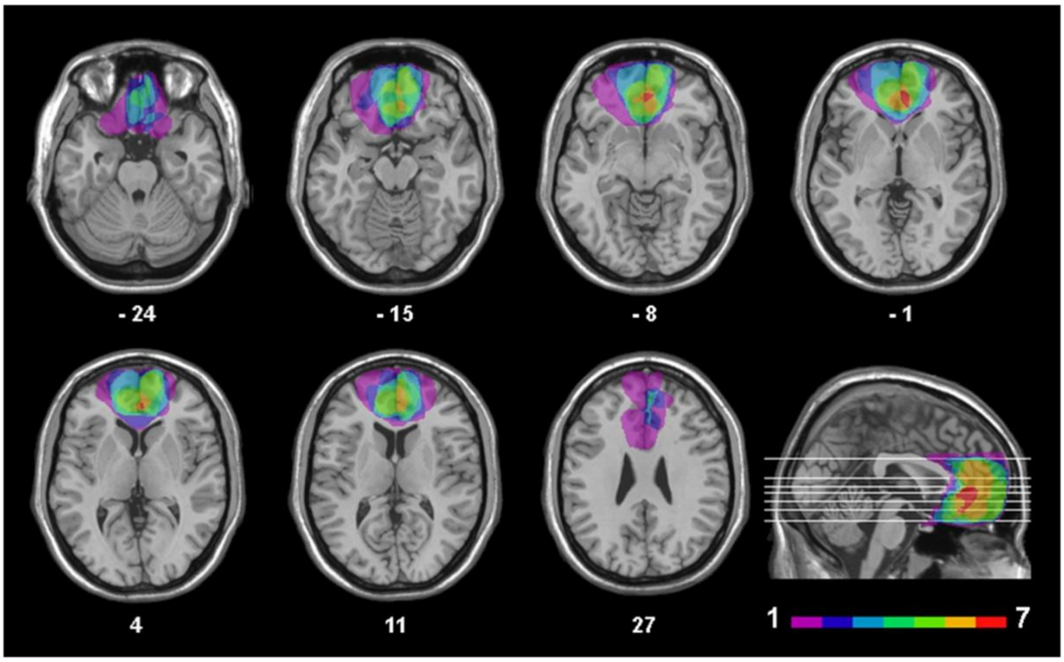

Figure 7. Extent and overlap of brain lesions. The figure represents vmPFC patients' lesions projected on the same seven axial slices and on the sagittal view of the standard Montreal Neurological Institute brain. The white horizontal lines on the sagittal view are the positions of the axial slices, 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 BA 11, 10, and 32. The left hemisphere is on the left side.

6.2.3 Scene construction task

We used a scene construction task adapted from Hassabis et al. (2007b). In all trials, participants were required to imagine novel experiences in as much detail as possible in response to short cue descriptions, read by the experimenter, and referring to 11 scenarios. Six out of the 11 scenarios required to imagine fictitious experiences, with no requirement for MTT, 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’, ‘beach’, ‘museum’, ‘pub’, and ‘forest’ scenarios used in Hassabis et al. (2007b). Differently, five out of the 11 scenarios required to imagine 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), plus two scenarios we added in order to match the number of future and fictitious scenarios more closely and compare the two types of scenario. Whereas the future scenarios in Hassabis et al. (2007b) were generally located in the near future (within the next year), the items we added refer to a farther future (10 years) (“Imagine something that will happen while you take a walk in your home town in 10 years…”, “Imagine your birthday in 10 years…”).

Participants described the imagined experiences until they came to a natural end. In line with Hassabis et al. (2007b), the examiner (author F.A.), blind to the hypotheses of the study (but not to group membership), 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 (1, “I did not feel like I was there at all;” 5, “I felt strongly like I was really there”), perceived salience (1, “I couldn’t really see anything;” 5, “extremely salient”), difficulty (1, “very easy”; 5, “very difficult”), and similarity to a memory (1, “nothing at all like a memory”; 5, “exactly 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 (see below).

To avoid fatigue, participants were generally tested in two separate sessions, about one week apart. Each session contained a similar number of future and fictitious scenarios, and the order of administration of the scenarios was randomized for each participant. Two healthy controls and two control patients were not available to be tested in two different days, and therefore received the two testing sessions in the same day, with an interval of about 3 hours. Testing sessions were recorded to enable transcription and later scoring of participants’ reports.

6.2.4 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 ranges between 0 and 8), spatial coherence index (score ranges between 0 and 6), and quality judgment (score ranges between 0 and 18). A description of each subcomponent is included in the next paragraphs.

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, e.g., objects, people, animals present in the scenarios), sensory descriptions (SD, e.g., “the chair is made of wood”), spatial references (SPA; e.g., “behind the bar”), and thoughts/emotions/actions (TEA, e.g., “I felt lonely”). For each subcategory, details were summed and the score was capped at a maximum of 7. Therefore, the total possible content score for each experience was 28 (note, however, that we obtained similar results using the uncapped data) (Hassabis et al., 2007b).

The spatial coherence index (SCI), a measure of the spatial integrity of the imagined scene, was derived from the responses to 12 questions requiring patients 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 wasn’t 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 score so as not to overpenalize fragmented descriptions (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 (QJ) is the scorer's assessment of the overall quality of the constructed experience. The scorers were requested to rate how well they felt the description induced a detailed ‘‘picture’’ of the scenario in their own mind’s eye. Originally ranging from 0 (no picture at all) to 10 (extremely rich picture) to avoid a complicated rating, the QJ was rescaled between 0 and 18 to be included in the EI calculation (see Hassabis et al., 2007b). We calculated the EI separately for fictitious and future scenarios. Two raters, blind to the aim of the study and to group membership, independently scored the scenarios of all but 2 participants (one of the two scorers was no longer available at the time the last two participants were tested). Agreement between scorers was high (Cronbach's $\alpha \geq 0.83$ in all cases). The average scores from the two scorers or the single scores (in 2 cases) were subjected to statistical analyses.

6.2.5 Statistical analyses

The dependent variables violated in most cases normality or homoscedasticity assumptions and therefore the data were analyzed using non-parametric tests. Kruskal–Wallis one-way ANOVA were used to assess group differences. Subsequently, to determine which group difference drove the main effects, we used Mann–Whitney's z-tests between each patient group and the control group and between the two patient groups as post hoc tests. To assess differences in performance between future and fictitious conditions within individual groups, we used the Sign test. To compare the difference in performance between future and fictitious scenarios across groups, we calculated, for each relevant measure and each participant, the difference (Δ) in the scores attained in fictitious vs. future scenarios. For example, the difference in the experiential index (EI) was calculated as Δ_{EI} = EI for fictitious scenarios – EI for future scenarios. Δ-scores, too, were analyzed using Kruskal–Wallis one-way analyses of variance, and Mann–Whitney's z-tests as post-hoc tests. In all cases, we report the two-tailed significance value.

6.3 Results

Considering the three original near-future items and the two far-future items we added separately did not change our results meaningfully, and therefore, for clarity, we present the results collapsed across the five future scenarios. It is worth noting, however, that participants (1.45 vs. 1, Sign test: $z = 3.34$, $p = 0.0008$), including vmPFC patients (2.5 vs. 1.86, Sign test: $z = 2.04$, $p = 0.04$), rated imagining far-future events as more difficult than imagining near-future events. This finding is worth noting: it suggests that participants did indeed attempt MTT, and did so towards specific points of subjective time, showing a good comprehension of task requirements. Far-future events, however, were also rated as more similar to a memory than near-future events (2.9 vs. 2.03, Sign test: $z = 4.40$, $p = 0.00001$). Possibly, individuals tended to solve the harder problem of imagining far (compared to near) future events by resorting to memories of past events to a greater extent. This precluded a direct comparison of far-future and near-future events. An analysis of the content of vmPFC patients' constructed future and fictitious experiences excluded the presence of (provoked) confabulation: in all cases, patients imagined future and fictitious experiences congruent with their possible future actions (as confirmed by family members) and with the suggested settings.

6.3.1 Experiential Index

Figure 8 and Table 5 show the Experiential index (EI) by participant group and type of scenario, and Tables 6a and 6b show examples of constructed future and fictitious experiences in vmPFC patients and healthy as well as brain-damaged controls. As is evident, vmPFC patients showed a reduced EI in both fictitious and future scenarios compared to the control groups. The ANOVA on the EI for future scenarios revealed a significant effect of Group (H = 11.02, p = 0.004). Post hoc comparisons showed that vmPFC patients had a reduced EI for future scenarios compared to healthy controls (z = -3.38, p = 0.0002), and control patients (z = -2.38, p = 0.02), whereas there were no differences between healthy controls and control patients (p = 0.65). The same analysis on the EI for fictitious scenarios revealed similar results: There was a significant effect of Group (H = 9.82, p = 0.007), indicating that vmPFC patients had a reduced EI compared to healthy controls (z = -3.30, p = 0.0003), and control patients (z = -2.06, p = 0.04), with no differences between the control groups (p = 0.86). Importantly, the EI for future and fictitious scenarios were highly correlated in either vmPFC patients ($r_{Spearman}$ = 0.86, p = 0.01), control patients ($r_{Spearman}$ = 0.80, p = 0.01), and healthy controls ($r_{Spearman}$ = 0.62, p = 0.03). These findings confirm that imagining fictitious and future experiences share important cognitive bases, and indicate that the vmPFC is crucial for both abilities.

Figure 8, however, also suggests that constructing rich future experiences posed challenges to vmPFC patients beyond those involved in constructing fictitious experiences. Indeed, the EI for future scenarios was significantly lower than that for fictitious scenarios in vmPFC patients (z = 2.27, p = 0.02), but not in healthy controls (p = 0.39) or control patients (p = 1). In order to compare directly the differences between imagining fictitious and future experiences across participant groups, we focused on the Δ_{EI} ($EI_{Fictitious}$ - EI_{Future}). There was a significant difference in Δ_{EI} across groups (H = 8.32, p = 0.02): Δ_{EI} was significantly higher in vmPFC patients than in healthy controls (z = 2.70, p = 0.005) or control patients (z = 2.17, p = 0.03), whereas no significant differences emerged between the control groups (p = 0.28). Thus, even though the vmPFC patients were generally impaired at imagining novel experiences, these patients were relatively more impaired at imagining future compared with fictitious experiences.

Having established that the EI is reduced in vmPFC patients, in the following sections we focused on the EI subcomponents separately, to qualify vmPFC patients' scene construction impairment, as well as the possible source for their relative disadvantage in constructing future vs. fictitious experiences.

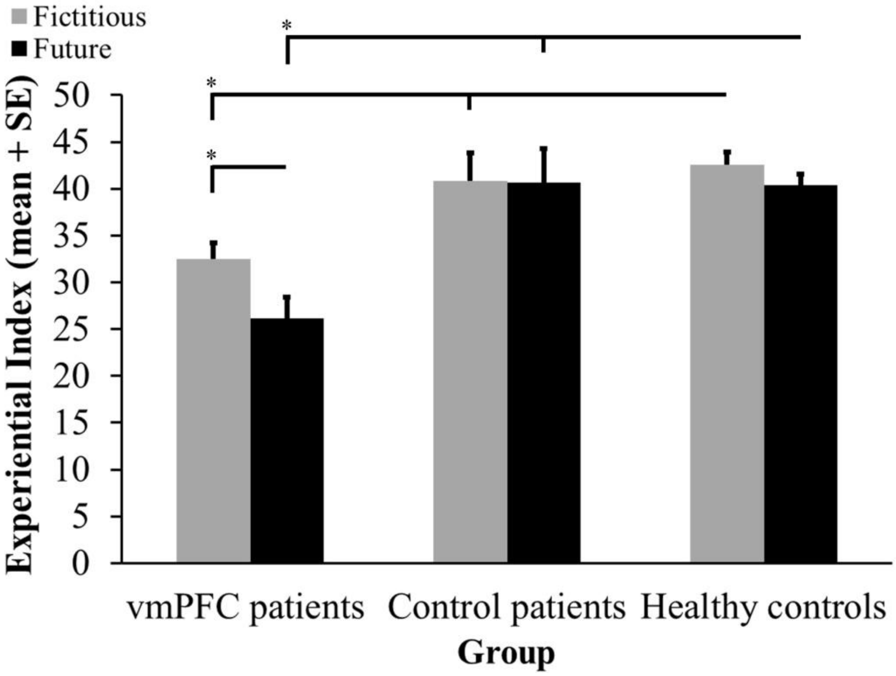

Figure 8. Mean Experiential Index scores by participant group and type of scenario. Bars represent standard errors of the mean (SE). * $p < 0.05$.

Table 5. Constructed experience performance

	vmPFC patients		Control patients		Healthy controls	
	Fictitious	Future	Fictitious	Future	Fictitious	Future
EI	32.52(1.73)	26.15(2.27)	40.87(2.98)	40.70(3.56)	42.57(1.35)	40.41(1.17)
Contents						
EP	4.82(0.37)	4.21(0.32)	5.24(0.47)	5.35(0.48)	6.34(0.19)	5.69(0.30)
SPA	1.26(0.18)	0.94(0.13)	2.17(0.46)	2.58(0.56)	2.15(0.32)	2.42(0.28)
TEA	5.79(0.45)	5.59(0.49)	6.05(0.62)	6.27(0.33)	6.64(0.20)	6.74(0.13)
SD	5.81(0.11)	3.71(0.49)	5.64(0.52)	5.29(0.54)	6.26(0.31)	5.66(0.34)
QJ	8.72(0.50)	6.38(0.77)	12.07(1.01)	11.72(1.21)	12.85(0.54)	12.09(0.36)
Ratings						
Sense of Presence	2.74(0.26)	2.57(0.23)	3.17(0.22)	3.27(0.23)	2.99(0.15)	2.93(0.11)
Perceived salience	2.64(0.22)	2.29(0.21)	3.00(0.17)	3.04(0.25)	3.00(0.17)	2.85(0.16)
SCI	0.74(0.34)	0.46(0.29)	3.54(0.51)	3.18(0.64)	2.35(0.35)	2.02(0.32)
Difficulty	1.86(0.22)	2.11(0.34)	0.78(0.24)	0.76(0.19)	1.14(0.23)	0.98(0.19)
Similarity to a memory	2.62(0.12)	2.74(0.15)	2.43(0.27)	2.24(0.29)	2.72(0.12)	2.27(0.17)

Note. EI = Experiential Index, EP = Entity Presence, SPA = Spatial Reference, TEA = Thought/Emotion/Action, SD = Sensory Description, QJ = Quality Judgment, SCI = Spatial Coherence Index. The values in brackets are standard errors of the mean.

Table 6a. Examples of fictitious constructed experiences from two vmPFC patients (P1 and P2), a healthy control subject, and a brain-damaged subject. We use brackets to indicate information added to clarify the significance of some detail, or when omitting information that may help identify individual patients. We use brackets to highlight the experimenter's statements (in Italics).

	vmPFC patients	Control patient	Healthy control
Age	P1: 45; P2: 42	42	51
Education	P1: 12; P2: 13	8	13
Fictitious scenario: Imagine you're standing in the middle of a bustling street market. Describe the experience and the surroundings in as much detail as possible using all your senses including what you can see, hear and feel.			
	P1 It's a market and it's full of people. Many women buying what they need, and little boys returning home from school. Going further I stop by a place where they sell sweaters, very nice yet cheap sweaters*…[Can you tell me more details about this?]* People are just normal, and they check out the stalls, for what is cheaper. And at the stand I stopped by there were highly embellished sweaters, decorated sweaters… *[Anything else you want to tell me about this scenario?]* There were a lot of people. That's it. Dressed rather conventionally, as one does when they go to the market. And each of them buys stuff. P2 I imagine there are people chatting, people buying and people selling. Some vendors, persons shouting, a bunch of passers-by who are there because of curiosity. I imagine there are some thin and tall immigrants selling their products and I imagine there is a noisy and chaotic environment, and I am forced to say "excuse me" a hundred times in order to get through. I also notice that people are very impolite in how they behave, they do not care about other people, or whether people have mental or physical disabilities, like I do. And I imagine people celebrating, I would say… *[Can you tell me more details about this?]* I imagine I am not alone, my significant other is with me and some other friends, and we will get lost for sure. I imagine there are a lot of people who sell any kind of items, also silly things, those useless objects… and the car traffic. And I imagine that the square or the main avenues are closed to the traffic.	It is a market located at the waterfront by the sea, a second-hand market, and in addition there are small stands with typical regional specialties. One walks in the middle of the crowd of people who are looking for things they need. Passing by the stands of typical, local, or regional stuff, one can smell diverse odors of different regions, tasting… Going on along the waterfront, looking at the sail boats and arriving at the end and after, we decide to come back and do another tour of smells, and sensations…The various ways to speak between people, other languages, and then continuing to walk*…[Can you tell me more details about this?]* The market is wide, located in a wide part of the quay at the waterfront with all stands situated on one side of the sea. They form like a barrier, and people in front of them, again on the waterfront, are speaking and engaging in conversation, they speak with the street traders. They trade pieces of cheese, of salami, and olives, tasting... *[Is there anything else you want to tell me about this?]* At a certain point we can hear the fanfare advancing, we turn our gaze towards the city square and we see the Bersaglieri (a corp of the Italian Army) moving forward with the brass-band, the guard of honor. And at the end they introduce themselves and there is the captain giving orders and the soldiers marching which itself sounds like music. All people clap their hands and in the middle of the crowd we make our way and we go back.	I don't like crowded market areas because the idea of a market is something narrow. There are people who push you and don't let you look at anything in peace. In order to pass you have to push, so the market is a not really a nice scenario. A narrow street full of nice things on the right and on the left. Things like fruits and vegetables, fish, meat, clothes, or gifts. You pass by and you have the desire to stop for a moment to get a better look at an item, in order to buy it, then it becomes a pain, because then there's that person who pushes you, that one who won't let you pass, won't let you look around. The owner of the stall is completely busy with many customers and doesn't pay attention to you. Sure, the market is a nice place, it's a pity that there are so many people. There should be more space. You walk, trying to elbow your way through. Then you get to a more open area where you can breathe more easily. I imagine in this place, a bit more open, a church or a building that, seen from outside, is a bit neglected and nobody looks at it, nobody pays attention to it. But then you manage to go inside and see that it is a very beautiful building, where you can see history with your own eyes. You discover paintings and see beautiful sculptures, which nobody pays any attention to, but they are part of the history of the city that you're in. They are absolutely there and they remind you that this city and that square, that open space, has been a very important place in the past centuries of the history of this city.

Table 6b. Examples of future constructed experiences from two vmPFC patients (P1 and P2), a healthy control subject, and a brain-damaged subject. We use brackets to indicate information added to clarify the significance of some detail, or when omitting information that may help identify individual patients. We use brackets to highlight the experimenter's statements (in Italics).

	vmPFC patients	**Control patient**	**Healthy control**
Age	P1: 45; P2: 42	42	51
Education	P1: 12; P2: 13	8	13
Future Scenario: Imagine the next time you'll meet a friend. Describe the experience and the surroundings in as much detail as possible using all your senses including what you can see, hear and feel.			
	P1 I usually meet my friend at home or at the bar. We have a coffee or an "ammazzacaffè" (something typically alcoholic drank after coffee), and we then decide what to do and where to go… *[OK, try to imagine the event of meeting a friend in the future, imagine the scene, and tell me all that you can about it]*. So, I meet a friend, and we go to the bar, then we decide where to go. Each of us could go with their partners. P2 I imagine meeting him and say Hi, but in fact I do not remember his name. I know many people so it's easy to forget their names. I ask how it is going… *[Tell me more details about this]* We see each other in viale Roma, (name of P2'city)'s principal street. I imagine he is really keen to chat with me, but I am in a hurry instead, because my companion wants to go home soon, absolutely. I would love to stay and have a chat… *[Can you tell me more details about this?]* I imagine meeting him in front of the schools. There is an elementary school right there, and a kindergarten in front of it. I imagine a relaxed chat with this guy.	I hope I am going to meet him by the beach. It's been a long time since we have seen each other, almost 1 year. We hug each other, we kiss, we say hi. We talk about what has been going on during the past year, he gives me his news, I give him mine. We go to a kiosk, we drink something together. It's full of people smoking, which bothers me a lot. We stay there anyway, for the sake of being together, even though we are in the middle of too many people, and it is chaotic. And we talk, and talk, and talk. We then stop drinking, and take our shoes off, and roll up our pant legs, to go and see whether the water in the sea is warm or chilly. We stay with our feet immersed in the water for a while, still talking, and looking around to see whether someone else is around. Someone we know, or interesting to look at. Then we go back on the beach and we tap our feet to each other, this way (he imitates the gesture), to remove the sand, we put our shoes on again, and we head to the centre of this little city. We look at the stores, the people, the confusion. Another bar and another drink, and we meet other friends, we talk and we have fun, we whistle to some girl passing by. Then the wives come, and everybody goes back to being serious immediately. They have come to rescue us, we go back to the cars, greeting each other.	I meet him at school, he comes to my school to meet me. I'm working, I'm in the classroom, I'm teaching and there's this friend of mine arriving that I haven't seen in a while, and he's there to see me. Together we finish the lesson that I was teaching my students and afterwards we start to talk about our common past, about what we've been doing, and we laugh and joke. We talk about what's happened since we've grown apart. His life, what he's been doing, whether he's married, what kind of job he has, whether he likes the job he has. Obviously, I also tell him whether I'm married, whether I'm divorced; what job I have, whether I like it or not. Whether I should have done something else. Then, maybe I'm done teaching, I'm free, and we leave the school. Instead of having the usual coffee, I invite him to my place for lunch and we have lunch together. I don't live in a big apartment, it's just the right size. We go there, we hang around a bit, and finally we put together something to eat between laughs and pats on the shoulders. We sit down at the table. We have lunch talking about the old times and many other things. Then, after lunch we might go out, we each do our own thing and we go for a drink. Then we say goodbye and we set a date for another meeting. We promise to see each other again soon, to have another lunch, a dinner, or go out, or something along those lines.

6.3.2 Spatial Coherence Index

We first focused on the spatial coherence index (SCI; see Table 5). There was a significant effect of Group for future scenarios ($H = 11.36$, $p = 0.003$). Post hoc comparisons showed that vmPFC patients had a reduced SCI for future scenarios compared to healthy controls ($z = -2.75$, $p = 0.004$), and control patients ($z = -2.86$, $p = 0.002$), with no differences between control patients and healthy controls ($p = 0.17$). Similar results were obtained for fictitious scenarios: There was a significant effect of Group ($H = 12.30$, $p = 0.002$), such that vmPFC patients had a reduced SCI compared to healthy controls ($z = -2.66$, $p = 0.005$), and control patients ($z = -2.91$, $p = 0.002$), with no differences between the control groups ($p = 0.06$). We found no significant differences on SCI scores for future and fictitious scenarios across groups ($p > 0.07$). These results show that vmPFC patients' constructed experiences were significantly more spatially fragmented than those of the control groups across all types of scenario.

6.3.3 Content Subscales

For future scenarios, there were differences across groups in the number of spatial references (SPA) ($H = 9.40$, $p = 0.009$), and, marginally, sensory descriptions (SD) ($H = 5.93$, $p = 0.05$) (see Table 5). vmPFC patients provided fewer SPA than healthy controls ($z = -3.04$, $p = 0.001$) and control patients ($z = -2.28$, $p = 0.02$), and fewer SD than healthy controls (SD: $z = -2.53$, $p = 0.01$), whereas control patients did not differ significantly from healthy controls ($p > 0.91$ in both cases). No significant group differences emerged in the number of thoughts/emotions/actions (TEA) and entity presence (EP) ($p > 0.059$ in both cases).

For fictitious scenarios, there were differences across groups in the number of EP ($H = 9.32$, $p = 0.009$), and, marginally, TEA ($H = 5.88$, $p = 0.05$): vmPFC patients produced fewer EP and TEA details compared with healthy controls (EP: $z = -3.13$, $p = 0.0007$; TEA: $z = -2.28$, $p = 0.02$), whereas no other significant differences emerged ($p > 0.06$ in all cases) (see Table 5). There were not significant group differences in the number of SD and SPA ($p > 0.07$).

Comparing participants' performance in future vs. fictitious scenarios revealed one first source for the relative disadvantage in EFT observed in vmPFC patients: vmPFC patients imagined fewer SD (Sign test: $z = 2.27$, $p = 0.02$) and EP (Sign test: $z = 2.27$, $p = 0.02$) in future compared to fictitious scenarios, whereas this difference was not found in control patients ($p > 0.72$ in both cases) and healthy controls ($p > 0.14$ in both cases). There was a significant difference across groups in the Δ_{SD} ($H = 8.56$, $p = 0.01$), which was higher in vmPFC patients than in healthy controls ($z = 2.37$, $p = 0.02$) and control patients ($z = 2.80$, $p = 0.003$), but comparable between the control groups ($p = 0.75$), confirming more marked difficulties at producing sensory descriptions for future vs. fictitious scenarios in vmPFC patients. No significant differences across groups emerged in the Δ_{EP} ($p = 0.08$).

6.3.4 Quality judgment

Consistent with the results on the specific contents produced by participants, we also found a significant difference in quality judgment (QJ) across groups in both fictitious ($H = 11.03$, $p = 0.004$), and future scenarios ($H = 12.09$, $p = 0.002$). In both cases, vmPFC patients attained a lower QJ than both control patients (fictitious: $z = -2.28$, $p = 0.02$; future: $z = -2.70$, $p = 0.005$) and healthy controls (fictitious: $z = -3.38$, p

= 0.0001; future: z = -3.55, p = 0.00004), whereas no differences emerged between the control groups (p > 0.65 in both cases) (see Table 5). Again, vmPFC patients received a lower QJ when imagining future compared to fictitious scenarios (Sign test: z = 2.04, p = 0.04), whereas both control patients' (p = 0.50) and healthy controls' reports (p = 0.15) were rated similarly across conditions. Group differences in Δ_{QJ} approached significance (H = 5.87, p = 0.05): vmPFC patients' Δ_{QJ} differed significantly from that of healthy controls (z = 2.37, p = 0.02), and marginally from that of control patients (z = 1.85, p = 0.07). No significant difference was found between the control groups (p = 0.70).

6.3.5 Participants' Ratings

6.3.5.1 Sense of presence and perceived salience

No significant group difference emerged for sense of presence or perceived salience, neither for the future (sense of presence: p = 0.13, perceived salience: p = 0.06) nor for the fictitious condition (sense of presence: p = 0.41, perceived salience: p = 0.27) (see Table 5). Sign tests did not reveal significant differences in sense of presence or perceived salience between future and fictitious scenarios across groups (p > 0.13 in both cases).

6.3.5.2 Task difficulty and similarity to a memory

The analysis on difficulty revealed group differences for imagining both future and fictitious experiences (future: H= 10.59, p = 0.005; fictitious: H = 7.69, p = 0.02), such that vmPFC patients found imagining novel experiences as more difficult than control patients (future: z = 2.86, p = 0.002; fictitious: z = 2.49, p = 0.01) and healthy controls (future: z = 2.75, p = 0.004; fictitious: z = 2.15, p = 0.03), whereas no significant differences emerged between the control groups (p > 0.31 in both cases) (see Table 5). Sign tests did not reveal significant differences in self-assessed difficulty between future and fictitious scenarios across groups (p > 0.44).

There were no group differences in ratings of similarity to a memory (p > 0.18), and no difference between future and fictitious scenarios within single groups (Sign test: p > 0.44 in all cases). Thus, consistent with EI scores, vmPFC patients found imagining novel experiences as more difficult than did the control groups. vmPFC patients occasionally complained about their problems at imagining novel experiences. One patient, G.V., commented that the task was difficult, and also “pointless” to him. “Even though I will try and think of a future event” - he said – “there is nothing like that in my life; I never imagine future events. What for?”

Importantly, vmPFC patients did not try to overcome the perceived difficulty at imagining novel events by creating experiences more similar to actual memories than did the controls groups, which would have complicated the interpretation of our results.

6.3.6 Future vs. fictitious cues

Even though construction of future and fictitious scenarios was matched for difficulty (see 6.3.5.2), fictitious cues point to specific places (e.g., market), whereas future cues are more vague in this respect (e.g., next weekend) (see Hurley et al., 2011 for a discussion). Because spatial locations are a particularly powerful retrieval cue (Robin and Moscovitch, 2014), we conducted additional analyses to make sure that vmPFC patients’ lower performance in future vs. fictitious scenarios was not due to problems in accessing specific places to stage future experiences. First, vmPFC patients mentioned the place in which the future experience occurred in most trials (91%), as did the control groups. Importantly, we restricted our analyses to future trials in which a specific place was mentioned, and confirmed our results: vmPFC patients attained a lower EI for future than fictitious experiences ($z = 2.27$, $p = 0.02$), whereas the control groups did not ($p > 0.38$ in both cases). These findings were confirmed by analyses on the Δ_{EI}, which was larger in vmPFC patients than in controls (vmPFC patients vs. healthy controls: $z = 2.45$, $p = 0.01$; vmPFC patients vs. control patients: $z = 2.06$, $p = 0.04$). Moreover, vmPFC patients ($z = 2.27$, $p = 0.02$), but not the control groups ($p > 0.38$ in both cases), produced fewer SD for future than fictitious scenarios, and the Δ_{SD} was larger in vmPFC patients than in controls (vmPFC patients vs. healthy controls: $z = 2.28$, $p = 0.02$; vmPFC patients vs. control patients: $z = 2.80$, $p = 0.003$). Additionally, in our set of future scenarios one item mentioned a specific place ("Imagine something that may happen to you in 10 years while you are taking a walk in your hometown"). Still, the EI for this scenario was lower than that for fictitious scenarios in vmPFC patients ($z = 2.27$, $p = 0.02$), but not the control groups ($p > 0.77$ in both cases).

6.3.7 Event construction and neuropsychological abilities: exploratory analyses

We ran Spearman correlation analyses between neuropsychological measures and the EI, separately for future and fictitious and scenarios. We found a significant, negative correlation between the number of errors in the Stroop task and the EI for both future scenarios ($r_{\text{Spearman}} = -0.78$, $p = 0.04$, *two-tailed*), and fictitious scenarios ($r_{\text{Spearman}} = -0.81$, $p = 0.02$, *two-tailed*).

6.3.8 Event construction and vmPFC: exploratory analyses

We investigated whether the EI for future and fictitious scenarios in vmPFC patients correlated with lesion volume. As anticipated, brain lesions in vmPFC patients overlapped maximally in BAs 11, 10, and 32. By using partial correlation analyses, we investigated the relation between the EI and lesion volume in each of the three BAs, partialing out the effect of lesion volume in the other two BAs, separately for future and fictitious scenarios.

We found that lesion volume in BA 11 correlated strongly with the EI for future scenarios ($r = -0.98$; $p = 0.003$, *two-tailed*), and, though marginally, with the EI for fictitious scenarios ($r = -0.84$; $p = 0.07$, *two-tailed*): the larger the lesion, the more pronounced the difficulties at constructing novel experiences. Lesion volume in BA 32 correlated with the EI for future scenarios ($r = -0.95$; $p = 0.01$, *two-tailed*), but not for fictitious scenarios ($r = -0.45$; $p = 0.44$, *two-tailed*), suggesting that BA 32 has a more prominent role in imagining personal future experience than fictitious experiences. Interestingly, lesion volume in BA 10 correlated positively with the EI for future scenarios ($r = 0.92$; $p = 0.02$, *two-tailed),* such that patients with bigger lesions were relatively less impaired at imagining future experiences. There was no relation between lesion volume in BA 10 and the EI for fictitious scenarios ($r = 0.31$; $p = 0.61$).

6.4 Discussion

In this study, vmPFC patients, control patients with lesions mainly in posterior cortices, and healthy controls, imagined personal, future experiences as well as fictitious, atemporal experiences. We found that constructed experience was, in both cases, poor in vmPFC patients compared to healthy and brain-damaged controls, as indicated by a severely reduced EI. This result is not likely to be due to reduced verbal fluency in vmPFC patients: first, verbal fluency was within the normal range in vmPFC patients, and matched between vmPFC patients and control patients, who had a normal EI. Second, neither phonemic nor semantic fluency correlated with the EI for future or fictitious scenarios in vmPFC patients ($p > 0.64$ in all cases). Additionally, for both future and fictitious scenarios, vmPFC patients also evinced a low spatial coherence index, and this measure does not rely on narrative abilities.

The finding that vmPFC patients were impaired at imagining both future and fictitious experiences indicates that vmPFC supports constructive processes necessary for, but not uniquely related to, EFT (Hassabis and Maguire, 2007; Schacter et al., 2012). One candidate process is scene construction, the cognitive ability grounding vivid imagination and experience of complex events, be these personally-relevant and located in subjective time, or purely fictional and atemporal (Hassabis and Maguire, 2007). To give rise to a recollection-like experience, indeed, any simulated experience needs to be “staged” within a spatial context. vmPFC patients, indeed, rated their constructed experiences as less spatially coherent, and provided fewer spatial details, than did the control groups, indicating a difficulty forming integrated scenes. This finding is in line with fMRI evidence of consistent activation of the vmPFC during scene construction (Hassabis et al., 2007a), as well as other operations requiring scene construction, including episodic remembering and future thinking (Addis et al., 2007, 2009a; D’Argembeau et al., 2008, 2010b; Spreng and Grady, 2010; Schacter et al., 2012). Consistently, in a recent study we have found that vmPFC patients were equally impaired in remembering the past and imagining the future. Notably, patients were also impaired at imagining future experiences of close and distant others, consistent with the suggestion that vmPFC may have a general role in the construction of complex experiences, whether self-relevant or not (Bertossi et al., 2016b).

Together with fMRI evidence, these results indicate that the vmPFC is a crucial node in a network enabling construction of novel events (Hassabis and Maguire, 2007; Schacter et al., 2012), and contribute to reveal its functional architecture. As anticipated, both fMRI and neuropsychological studies indicate the MTLs as crucial neural substrates of scene construction (Hassabis et al., 2007a, 2007b). Few neuropsychological studies have focused on brain areas outside the MTLs. Berryhill and colleagues have shown that the posterior parietal cortex is necessary to imagine both future and fictitious experiences (Berryhill et al., 2010), consistent with fMRI evidence (Hassabis et al., 2007a). In that study, however, patients with lesions in the dorsolateral prefrontal cortex, which is not normally activated during scene construction (Hassabis and Maguire, 2007), were also impaired at imagining novel experiences. The authors, therefore, raised the concern that because constructed experience tasks are typically effortful any brain lesion may impair performance (Berryhill et al., 2010), making it difficult to trace brain-behavior relations. Our result that constructed experience was impaired in vmPFC patients but preserved in control patients argues against this possibility, and reinforce the hypothesis that vmPFC, the MTLs, and the posterior parietal cortex are crucial nodes of a well-delineated system engaged during event construction (Hassabis and Maguire, 2007). Consistently, vmPFC, the hippocampus, and the inferior parietal cortex participate jointly in a “MTL-subsystem” of the DMN supporting construction of mental scenes based on memory (Andrews-Hanna et al., 2010b).

Even though the present data fit with a “scene construction” account (Hassabis and Maguire, 2007), they are also consistent with the “episodic simulation hypothesis” (Schacter et al., 2008, 2012), according to which simulation of future (as well as fictitious) experiences relies on constructive processes necessary to make available and flexibly recombine all the relevant details constituting complex experiences (rather than assemble the spatial foundation for details to reside; Mullally and Maguire, 2013). In particular, Benoit and colleagues have recently demonstrated that vmPFC supports the simulation of novel episodes by coordinating, integrating, and summarizing knowledge about episodes’ elements, stored in distributed cortical regions (Benoit et al., 2014). vmPFC is implicated in strategic retrieval processes needed to constrain memory search, and monitor the appropriateness of recovered memories, operating during episodic (autobiographic) as well as semantic retrieval (Moscovitch and Melo, 1997; Gilboa et al., 2006). vmPFC, therefore, might work in concert with the MTLs during event construction, orchestrating search and integration of parts of episodic memories and semantic knowledge to combine into a novel event.

vmPFC and the MTLs likely differ in the nature and timing of their contribution to event construction, and future research should now be aimed at specifying the precise function of, and interplay between, nodes of the core network now known to be critical for event construction. Maguire and Mullally (2013) have proposed that the hippocampus drives an early, automatic scene construction process serving as the foundation upon which (re)constructed events unfold. Such a “spatial scaffold” appears of primary importance in guiding both retrieval of past events and the construction of novel events (Maguire and Mullally, 2013; Robin and Moscovitch, 2014; Robin et al., 2016). The spatial representation arranged by the hippocampus may then be fed back to other areas to perform additional integrative processes and express the subjective experience of the event. vmPFC is critical for appropriate processing of schema-related information (Burgess and Shallice, 1996; Ghosh et al., 2014), and represents abstract summaries of frequent events (Krueger et al., 2009). During scene construction, this region may help activate and maintain a stable schematic knowledge of relevant events (e.g., the typical birthday party, the typical market) around which to construct a specific event, and point to a set of related, context-relevant past experiences to use as source of details (Preston and Eichenbaum, 2013; Benoit et al., 2014). A comparison in the EI (collapsed across future and fictitious scenarios) between hippocampal patients (mean EI = 25.88; data averaged between Hassabis et al., 2007b; Mullally et al., 2012) and vmPFC patients (mean EI = 29.62; this study) suggests that hippocampal patients may be more impaired in scene construction than vmPFC patients, as expected if patients were deprived of even a rudimentary medium upon which to arrange individuals' details. vmPFC patients, on the other hand, may have succeeded at creating an initial scene, but failed at retrieving from memory and integrating successfully additional, multimodal details to make it a rich mental experience. We note that vmPFC patients did not endorse schema-irrelevant details. They recounted very typical birthday parties, weekends, pub experiences, market experiences, pub experiences, etc. (see Serra et al., 2014 for a discussion), though these experiences were poor in detail. It is possible, however, that vmPFC patients with spontaneous confabulation would provide experiences that would deviate from schema-related knowledge (Ghosh et al., 2014; Gilboa et al., 2006), and be highly implausible (see Cole et al., 2014).

Although our findings highlight a pervasive role of vmPFC in the imagination of novel experiences, they also suggest a more pronounced involvement in EFT. Indeed, vmPFC patients, but not the control groups, attained a significantly lower EI for future than fictitious scenarios. Future and fictitious scenarios were rated as equally difficult across groups, and, therefore, performance differences between future and fictitious scenarios observed in vmPFC patients cannot be attributed merely to task difficulty. In fact, vmPFC patients (as well as the controls groups) rated future and fictitious experiences as comparable in many respects, including spatial coherence and sense of presence. However, vmPFC patients (unlike the controls groups) imagined significantly fewer sensory details for future compared to fictitious experiences. As anticipated, beyond scene construction processes shared with imagining fictitious scenarios, EFT entails autonoetic awareness, a subjective sense of time typically accompanying MTT (Tulving, 1985), and is heavily constrained by self-knowledge (D’Argembeau and Mathy, 2011). These elements apply to imagining fictitious experience to a much lesser extent, if not at all. Autonoetic awareness has been long linked to the frontal lobe (Wheeler et al., 1997), which may explain why EFT proved especially challenging for vmPFC patients. A similar impairment in imagining future vs. fictitious scenarios, indeed, has been documented in older adults (Rendell et al., 2012), who show disproportionate prefrontal lobe atrophy (Raz et al., 2005).

EFT is also intimately linked to self-knowledge: it is through introspecting on who they were, are, and wish to become that individuals construe plausible personal future events. These must maintain a tie to past memories, representing their natural continuation, but also obligatorily deviate from them, to reflect changes in goals and preferences with time (Conway and Pleydell-Pearce, 2000). D’Argembeau and Mathy (2011) have shown that self-knowledge is crucial to frame search and integration of episodic details during EFT, as well as during episodic remembering. Knowledge about personal goals is especially effective in driving EFT. vmPFC patients' impairment in EFT, therefore, may be related to an inability to drive search processes appropriately based on relevant self-knowledge. vmPFC, indeed, supports self-referential processing (D'Argembeau et al., 2012; Philippi et al., 2012), and is more active during imagination of future events related (as opposed to unrelated) to personal goals (D'Argembeau et al., 2010b).

vmPFC patients' more severe difficulty at "seeing" the future (compared to the fictitious) had not been reported in patients with lesion to the MTLs (Hassabis et al., 2007b) or the posterior parietal cortex (Berryhill et al., 2010), and, therefore, may be a specific signature of vmPFC damage on EFT. This finding may relate to vmPFC patients' steep TD (Sellitto et al., 2010): patients may devalue future rewards because they cannot pre-experience their future richly, at least as richly as they can experience fictitious events (Boyer, 2008; Ciaramelli and di Pellegrino, 2011; Schacter et al., 2012). Steep TD, indeed, is not observed in MTLs patients (Kwan et al., 2013), who show impaired EFT (Klein et al., 2002; Race et al., 2011), but not a disadvantage in imagining their own future as opposed to purely fictional events (Hassabis et al., 2007b). It would be important to confirm vmPFC patients' imbalance in the construction of temporal vs. atemporal experiences in future studies probing construction of past, future and atemporal events within the same paradigm, and with more controlled cues. The cues we used were matched for difficulty, and we made sure that the presence of a precise location in fictitious vs. future cues was not the factor driving performance differences in vmPFC. However, some of the fictitious cues contained information that may have been useful to prime associations (e.g., a bustling market, a tropical beach), at least in vmPFC patients. Using a more controlled set of cues will help determine whether temporality significantly and consistently interact with scene construction in these patients.

Despite gathered from a relatively small group of patients, correlation analyses suggest that general deficits in scene construction and specific deficits in EFT may have different roots within vmPFC. Lesion volume in BA 11 correlated negatively with the EI for both future and fictitious scenarios, suggesting that the most ventral part of vmPFC may mediate constructive processes needed to simulate any novel event. Differently, lesions in BA 10 and BA 32 had a more specific impact on the EI for future scenarios. Specifically, lesion volume in BA 10 correlated positively and lesion volume in BA 32 correlated negatively with the EI. Constructing truly novel events based on highly familiar cues (e.g., a birthday party) requires resisting interference from similar past memories. The EI, indeed, correlated with interference in the Stroop task. BA 10 is preferentially associated with retrieval of real (vs. imaginary) episodic memories (Hassabis et al., 2007a; Addis et al., 2009a). In the context of impaired strategic retrieval processes, a reduced input from BA 10 may have paradoxically protected vmPFC patients from memory-interference during EFT. On the other hand, the anterior cingulate region BA 32 is engaged while detecting response conflict, as in the Stroop task (Botvinick et al., 2004), and competition among memory traces (Kuhl et al., 2007). During EFT, therefore, BA 32 may help control interference from similar episodic memories, allowing construction of future events that are not a mere copy of the past, but reflect relevant, updated self-knowledge (e.g., goals).

We note that, in a recent report, patients with medial prefrontal lesions proved able to imagine future events (Kurczek et al., 2015). While differences between our results and the results by Kurczek and collaborators may depend on the site of brain lesions (i.e., centered on BA 11 in the present study and on BA 10 in Kurczek et al.'s study), the two studies also had important methodological differences. For example, in this study patients constructed “entire events”, in line with previous literature (e.g., Addis et al., 2009b, 2007; Hassabis et al., 2007b; Race et al., 2011), whereas in Kurczek et al. (2015) patients narrated circumscribed fragments of previously selected events. The two procedures likely placed different demands on event contruction processes.

To conclude, we have shown that vmPFC patients are impaired at imagining both future and fictitious experiences, indicating that vmPFC is necessary for the construction of novel experiences, including personal future experiences (EFT). vmPFC may support core construction/retrieval processes critical for EFT (e.g., scene construction). However, vmPFC patients' impairment was more marked for future than fictitious experiences, suggesting that vmPFC may mediate additional components of EFT, beyond core constructive processes. We propose that different regions within vmPFC support distinct component processes of EFT. BA 11 may underlie constructive processes needed to assemble and stage any complex experience: future as well as atemporal. BA 10 and BA 32, on the other hand, may be engaged specifically during simulation of those experiences that, considering our own history and current goals, most likely await us in the future.

7 Experiment 3 - Impaired future thinking following vmPFC damage: a deficit of prospection, narration, or scene maintenance?

7.1 Introduction

In order to construct a complex scenario it is necessary to combine different elements that compose the scenario in a coherent manner, maintaining a complex scenario in mind, and verbally describe it, creating an extensive narrative (Suddendorf and Corballis, 2007; Hassabis and Maguire, 2009). As we noted before (see 2.3), patients with lesions in the MTLs are impaired at remembering the past and imagining the future (Race, Keane, & Verfaellie, 2011; but see Squire et al., 2010). In that study, participants were shown drawings of scenes and they were instructed to tell a story about what was going on in the scenes. Patients and controls showed preserved ability to construct narratives (Race et al., 2011). In another study (Race et al., 2013), amnesic patients (with MTL lesions) and healthy controls were asked to describe pictures of scenes in as much detail as possible without creating stories. Patients and controls described a similar number of total details, suggesting that narrative descriptions were intact in amnesic patients.

However, other studies demonstrated that amnesic patients may perform poorly in describing complex scenes (Zeman et al., 2013). Zeman and colleagues asked amnesic patients and healthy participants to imagine complex scenes and describe two complex paintings and two real-life settings. Amnesic patients provided fewer details in imagining scenes and described fewer elements of the current scenes compared to healthy controls. Moreover, the superior performance of the healthy controls in the imagination condition became non-significant after controlling for performance in the scene description condition. These results show that amnesic patients deficit in imagining complex scenarios may be explained by a difficulty in describing any kind of experiences also when experiences are not imagined. In another study amnesic patients showed impoverished discourse integration abilities (Race et al., 2015). Narratives of remembered events and imagined future events provided by amnesic patients and healthy controls were analyzed using a scoring of narrative cohesion and coherence. For the “narrative cohesion scoring”, linguistic elements that work as a cohesive ties, such as pronouns and conjunctions (e.g., “My pencil is broken. I need a new *one*”), were counted. For the “narrative coherence scoring”, points were assigned to narratives oriented in time and space, considering the degree to which the actions could be ordered on a timeline, and the extent the narrator stayed on topic.

Amnesic patients produced fewer cohesive ties and they showed a reduced coherence score than healthy participants in both past and future narratives (Race et al., 2015). Together, these results suggest that the deficit in autobiographical memory and EFT shown in patients with lesions to a node of the DMN, such as MTLs, may be, at least in part, caused by non-episodic mechanisms, for example poor narrative abilities (Gaesser et al., 2011). Indeed, tasks that are often used to investigate autobiographical memory and EFT involve the creation of extended narratives.

It has been hypothesized that also executive functions may be crucial to sustain prospection (Addis et al., 2008; D’Argembeau et al., 2010a; Hill and Emery, 2013). For instance, in a study on young and old adults, working memory performance correlated with internal details produced during an EFT task and autobiographical memory retrieval (Zavagnin et al., 2016). In another experiment (Hill and Emery, 2013), participants completed measures of verbal and visuo-spatial working memory, as well EFT and episodic memory. In one task, participants were cued to recall specific events occurring in their personal past and imagine specific events that might occur in their personal future. The total number of specific events generated for each temporal condition was counted. The results showed that a composite score of working memory capacity was significantly correlated with future specificity (Hill and Emery, 2013). These findings demonstrate that working memory may support EFT and suggest that it is important to consider working memory capacity when EFT is investigated.

As we demonstrated before, the vmPFC plays a critical role in supporting the ability to construct past and future experiences (see Experiments 1 and 2). Potentially compromised narrative abilities, however, may be one factor hindering vmPFC patients' performance in recalling and imagining any type of event. In a study on older adults (Gaesser et al., 2011) who may show frontal atrophy (Raz et al., 2005), old and young participants described details about a picture or imagined future events using the picture as cue. A deficit in EFT was found in older adults who showed also poor abilities in describing pictures compared to young participants. Thus, the impairment in older adults in imagining the future may be explained, at least in part, by their poor narrative abilities.

In Experiment 2, however, we showed that vmPFC patients were more impaired at imagining future than fictitious experiences and this effect was not present in control patients and healthy controls. One may argue that vmPFC patients are impaired at imagining the future because vmPFC mediates other processes rather than episodic/constructive ones, such as working memory abilities, crucial for EFT. It is well known that the prefrontal cortex is involved in working memory performance (for a review see D’Esposito & Postle, 2015). The vmPFC activity, together with the activity of other brain areas, has been found relevant for executive processing in a working memory task. In a study Luu and colleagues (2014) employed EEG methodology for examining both the time course and cortical networks involved in working memory, as assessed by the n-back task. Before the stimulus onset, visual cortex network (pre-stimulus network), which includes also the posterior cingulate cortex, was found active reflecting anticipatory and attentional processes. Right after the stimulus onset, the vmPFC, together with other brain regions, becomes associated with the pre-stimulus network. This second network appears to reflect executive control processes, suggesting an involvement of the vmPFC in working memory. Considering also other experimental evidence (Barbey et al., 2009), authors hypothesized that the vmPFC may be critical for the maintenance, manipulation, and monitoring of information (Luu et al., 2014). In a study on Social Working Memory (SWM), that is the capability of maintaining and manipulating social information about others, for example personality traits and mental states (Meyer et al., 2015), participants encoded two, three or four of their friends' names, they were asked to rank the friends along a trait dimension during a delay period, and answered a true/false question about their rank order. In addition, participants completed classic working memory trials in which they reordered friends' names alphabetically during the delay period. The results identified regions that were more strongly increasing with SWM load level compared to load level in the classic working memory task, which involved the mentalizing network, including the vmPFC. Considering that vmPFC is engaged during SWM and that EFT often involves social information, a lesion to the vmPFC may affect working memory capacity and, in turn, performance in EFT tasks.

To date it is not clear whether the vmPFC mediates processes as working memory or narrative abilities that may explain vmPFC patients' impoverished capability of imagining future events. In the current study, we are firstly interested in replicating the results we found in experiment 1 on the role of vmPFC in imagining future experiences. Second, we investigated whether vmPFC patients' deficit in EFT may be due, at least in part, to a lack of narrative construction (narrative loss hypothesis) and/or an inability to maintain complex scenes in working memory (working memory loss hypothesis). To test these hypotheses, we asked vmPFC patients and healthy participants to imagine future episodes using pictures as cues and to perform a picture description task in two conditions: in the presence of a picture (description condition) and in absence of a picture after an observation phase (working memory condition). The results showed that the poor performance of vmPFC patients in imagining future events does not depend on a working memory loss or on a deficient capability of describing complex images. Indeed, group differences in imagining the future remained also when we controlled for these factors.

7.2 Methods

7.2.1. Participants

Participants included 6 patients with vmPFC damage (vmPFC patients) and 11 healthy individuals (see Table 7 for demographic information). Healthy individuals were matched to patients in terms of age (t = 0.45, p = 0.66) and education (t = 0.26, p = 0.79). Patients were recruited at the Centre for Studies and Research in Cognitive Neuroscience, Cesena, Italy. In all cases, vmPFC patients’ lesions were the results of the rupture of an aneurysm of the ACoA. Lesions were bilateral, though often also asymmetrical (see Figure 9). Patients taking part in the study were in the stable phase of recovery (at least 3 years post-morbid), 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).

Also, the healthy individuals were not taking psychoactive drugs, and were free of current or past psychiatric or neurological illness as determined by case 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 Ethical Committee of the Department of Psychology, University of Bologna.

7.2.1.1 Neuropsychological assessment

Patients' general cognitive functioning was generally preserved, as indicated by the scores they obtained in the Raven Standard Matrices (RMS) that were within the normal range, and similar between groups ($t = -1.62$, $p = 0.12$) (see Table 7).

vmPFC patients also received a more extensive neuropsychological evaluation aimed at qualifying their cognitive profile further. vmPFC patients reported normal scores in verbal short-term memory (Digit Span: Mean equivalent score (ES) = 3; note that the equivalent score ranges from 0 = impaired performance, and 1 = borderline performance, to 2 - 4 indicating normal performance) (Spinnler and Tognoni, 1987), spatial short-term memory (Corsi test: ES = 3.17), and working memory assessed with the 2-back task from the Test Battery for Attentional performance (TEA) (false alarms: $t = 37.5$, reaction times: $t = 42.8$, cut-off = 30) (Zoccolotti et al., 1994; Zimmermann and Fimm, 2002). Patients exhibited normal performance in several tests tapping executive functions, such as the Tower of London test ($t = 43.57$, cut-off = 30) (Culbertson and Zillmer, 2000), phonemic (ES = 2.17) and semantic fluency (ES = 2.83), and the Stroop test (mean number of errors = 0.91, cut off > 7.5) (Spinnler and Tognoni, 1987). vmPFC patients showed a borderline performance in the Wisconsin Card Sorting Test, which was characterized by many perseverative errors (t = 30.5, cut-off = 30), suggesting an impoverished cognitive flexibility. Long-term memory was weak, 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 and Tognoni, 1987).

Table 7. 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 brackets are standard errors of the mean.

7.2.2 Lesion analysis

Patients' individual lesions, derived from the most recent magnetic resonance imaging (MRI; N = 1) or computerized tomography (CT; N = 5) images, were manually drawn by a neurologist or by M.M. (both were not involved in the present study, and blind to task performance) and then verified by the same neurologist, directly on each slice of the normalized T1-weighted template MRI scan from the Montreal Neurological Institute provided with the MRIcro software (Rorden and Brett, 2000) (see also Karnath et al., 2004; Moro et al., 2008; Tsuchida and Fellows, 2012). This template is approximately oriented to match Talairach space (Talairach and 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 et al., 2007). MRIcro software was used to estimate lesion volumes (in cc) and to generate lesion overlap images.

Figure 9 shows the extent and overlap of brain lesions in vmPFC patients. BAs affected in the vmPFC group were areas BA 10, BA 11, BA 24, BA 25, BA 32, BA 46, BA 47, with region of maximal overlap occurring in BA 11 (M = 22.55 cc, SD = 8.80, about 34% of BA 11's volume), BA 10 (M = 14.14 cc, SD = 4.36, about 38% of BA 10's volume), and BA 32 (M = 9.25 cc, SD = 2.76, about 29% of BA 32's volume).

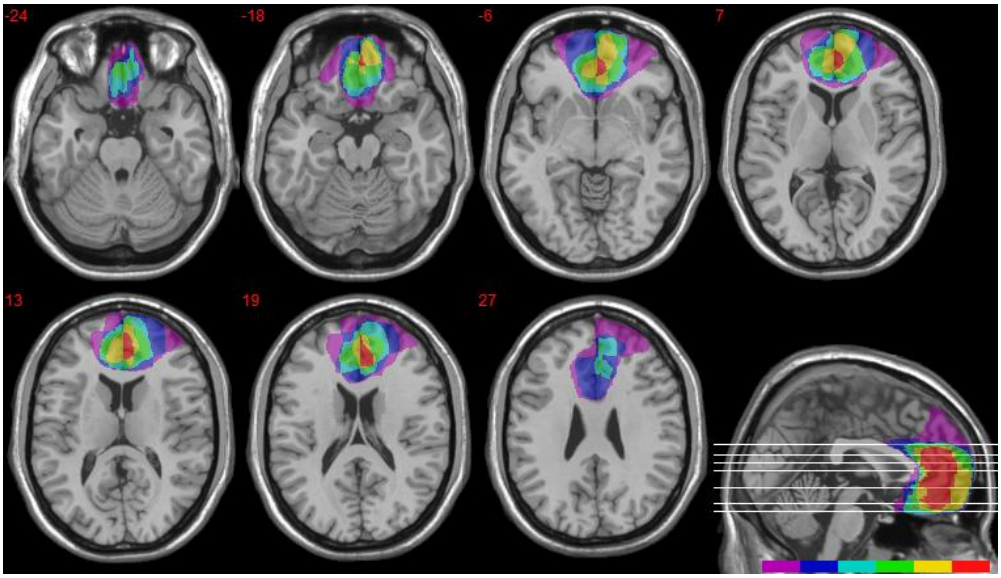

Figure 9. Extent and overlap of brain lesions. The figure represents vmPFC patients' lesions projected on the same six axial slices and on the sagittal view of the standard Montreal Neurological Institute brain. The white horizontal lines on the sagittal view are the positions of the axial slices, and 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 BA 11, 10, and 32. The left hemisphere is on the left side.

7.2.3 Stimuli

Eleven colored pictures (size, 640 × 480 pixels) were selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008). Pictures depicted people in different environments/situations: nine pictures were used in the main task (picnic, street, football field, park, office, sea, living room, fast food, and city) and two were used for the practice sessions (fishing and theater). We selected all pictures with positive valence (mean valence = 6.31, SD = 1.12). The 9 photographs used in the main part of the task were randomly assigned to the three conditions for each participant (3 pictures for each condition; see paragraph 7.2.4 for a description of the three conditions).

7.2.4 Experimental task

For each trial, participants completed a computerized adapted version of the Autobiographical Interview (Levine et al., 2002; Gaesser et al., 2011). Participants either imagined an event using the picture as cue (future condition), or described the details in picture in two conditions. In the description condition, participants described, verbally, details about a picture that remained on the screen for the entire duration of the description. In the working memory (WM) condition, participants first observed the picture for a maximum of 5 minutes. When participant felt ready to describe it, the picture was taken away and they were required to remember and verbally describe the elements in the picture. In the future condition participants were required to imagine three future events using the pictures as cues. In all conditions, participants provided as many details as possible for a maximum of 5 minutes per picture. Trials were blocked by condition to facilitate compliance with the instructions. Presentation order of conditions and pictures were randomized across subjects.

General prompts were given when necessary to clarify instructions or solicit further details. For description and WM trials, participants were required to describe the different people, objects, and environment in the picture and their relationship to one another (e.g. What are the people doing? What do they look like? Where are they?). Participants were instructed to report only what was depicted in the picture without embellishing. For future trials, participants imagined personal events that could possibly occur in the next 2-3 years with the picture as the general setting. Imagined experiences did not need to strictly involve the elements presented in the picture. Participants were instructed to experience events from a field perspective (through their own eyes) rather than from an observer perspective (from an external vantage point). Events generated for imagination trials were required to be specific in time and place, lasting several minutes to hours, but not exceeding a day.

After each trial in all conditions, participants were asked to answer three questions: (1) how detailed was the imagination of future event or the picture? (Detail: 1 – Not detailed at all; 4 – Very detailed); (2) How much were you touched by the event/the picture (Emotion: 1 – I was not touched at all; 4 – I was very touched); (3) How difficult was the task? (Difficulty: 1 – Very easy; 4 – Very difficult).

While imagining the future and describing the pictures, in both description and WM conditions, participants were recorded. The time participants employed to describe the future event and describe/observe the pictures, in both description and WM conditions, was also recorded.

7.2.5 Scoring

Participants' reports were recorded, transcribed, and scored using the Autobiographical Interview protocol developed by Levine et al. (2002) and adapted following the study by Gaesser and colleagues (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 items part of the picture were scored as external details for future condition trials so that only imagined future events were considered as internal details. The verbatim descriptions were scored as internal details for both description and WM conditions. Inferences about the picture (e.g. speculations, providing explanations for peoples' actions) were scored as external details for description trials in both description and WM conditions. For the WM condition, wrong elements remembered by participants were considered as external details (e.g., wrong position of the elements). Raters took into account the related pictures to classify details as internal or external information.

Two raters scored the transcripts independently. A main rater, blind to group membership and to the hypothesis of the study, scored all events/descriptions, and a second rater scored 62% of the events/descriptions. Inter-rater reliability for internal and external details between the two raters were assessed with intra-class correlation (McGraw et al., 1996), which indicated high agreement between the two scorers. Coefficient (Cronbach's α) for internal detail was 0.98 and for external detail was 0.89.

7.3 Results

7.3.1 Ratings

The mean ratings of Detail, Emotion, and Difficulty are presented in Table 8. We examined possible differences between groups on characteristics that could have influenced somehow the performance of participants in the task. Ratings did not always follow normal distribution (Kolmogorov-Smirnoff test: $d > 0.36$, $p < 0.05$), hence, group differences on ratings were analyzed using Mann-Whitney U tests. Across conditions, healthy controls and vmPFC patients gave similar ratings of Detail, Emotion, and Difficulty ($z > -1.75$, $p > 0.07$).

Table 8. Mean values of Detail, Emotion, and Difficulty ratings

	Future condition			Description condition			WM condition		
Group	Det	Emo	Diff	Det	Emo	Diff	Det	Emo	Diff
vmPFC	2.03(0.24)	2.42(0.33)	2.75(0.23)	2.53(0.27)	1.87(0.25)	2.10(019)	2.42(0.16)	1.65(0.21)	2.30(0.28)
HC	2.49(0.16)	2.92(0.21)	2.03(0.28)	3.05(0.05)	2.19(0.16)	1.94(0.17)	2.81(0.12)	1.88(0.23)	2.43(0.19)

Note. vmPFC = ventromedial prefrontal cortex; HC = Healthy controls; WM = working memory; Det = Detail; Emo = Emotion; Diff = Difficulty. The values in brackets are standard errors of the mean.

7.3.2 Duration of trials during future, description, and WM conditions

The mean values of response times that participants employed in performing each trial are presented in Table 9. Group differences were analyzed using t-tests because values did not violate normality assumptions. vmPFC patients and healthy controls needed a similar amount of time to imagine future events ($t = 0.44$, $p = 0.66$), to describe the pictures in the description ($t = -1.64$, $p = 0.12$), and in WM conditions ($t = -1.59$, $p = 0.13$). Groups did not differ in the amount of time they used to observe the pictures in the WM condition (t = -0.52, p = 0.61). These findings suggest vmPFC patients were not impulsive in providing their narratives, so they did not hasten to imagine future experiences or describe pictures, and that they took a sufficient amount of time to observe the pictures.

Table 9. Mean values of response times that participants employed to perform the task (in minutes)

	Future condition	Description condition	WM condition	
Group			Observation	Description
vmPFC	3.55(0.56)	2.25(0.40)	0.71(0.07)	1.44(0.26)
HC	3.29(0.31)	3.12(0.32)	0.86(0.19)	2.25(0.34)

Note. vmPFC = ventromedial prefrontal cortex; HC = Healthy controls; WM = working memory; Observation = phase of observation in working memory condition; Description = phase of description in working memory condition. The values in brackets are standard errors of the mean.

7.3.3 Details

The mean number of internal and external details across conditions are depicted in Figures 10 and 11. We assessed group differences in the number of details in future, description and WM conditions by conducting a 2 (Group: Healthy controls, vmPFC patients) × 3 (Conditions: Future, Description, WM) × 2 (Detail: Internal, External) ANOVA. Significant main effects of Group ($F_{(1,15)}$ = 11.25, p = 0.004) and Detail ($F_{(1,15)}$ = 10.60, p = 0.005) were qualified by a significant Group x Detail interaction ($F_{(1, 15)}$ = 4.68, p = 0.04). A Fisher post-hoc test showed that vmPFC patients provided fewer internal details compared to details provided by healthy controls in all conditions (11.50 vs. 28.54, p = 0.0004), however, no significant differences between groups emerged in the number of external details (p = 0.24). A main effect of Condition ($F_{(2,30)}$ = 4.12, p = 0.02) was qualified by a Condition x Detail interaction ($F_{(2,30)}$ = 19.41, p = 0.000004): both groups provided more internal details in the description (29.02 vs. 13.88, p < 0.000001) and WM (24.68 vs. 13.88, p = 0.00005) conditions than in the future condition, and more external details in the future condition compared to the WM condition (15.33 vs. 7.86, p = 0.0002). No other main effects or interactions were significant (all p values > 0.53).

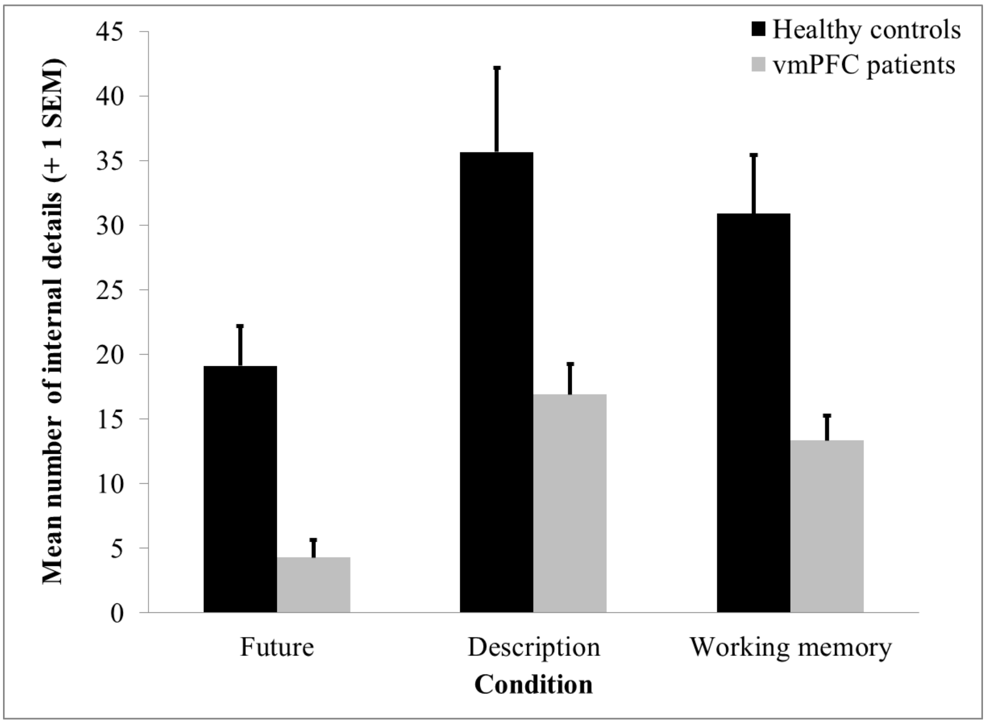

Figure 10. Mean number of internal details by participant group and type of condition. Bars represent standard errors of the mean (SEM).

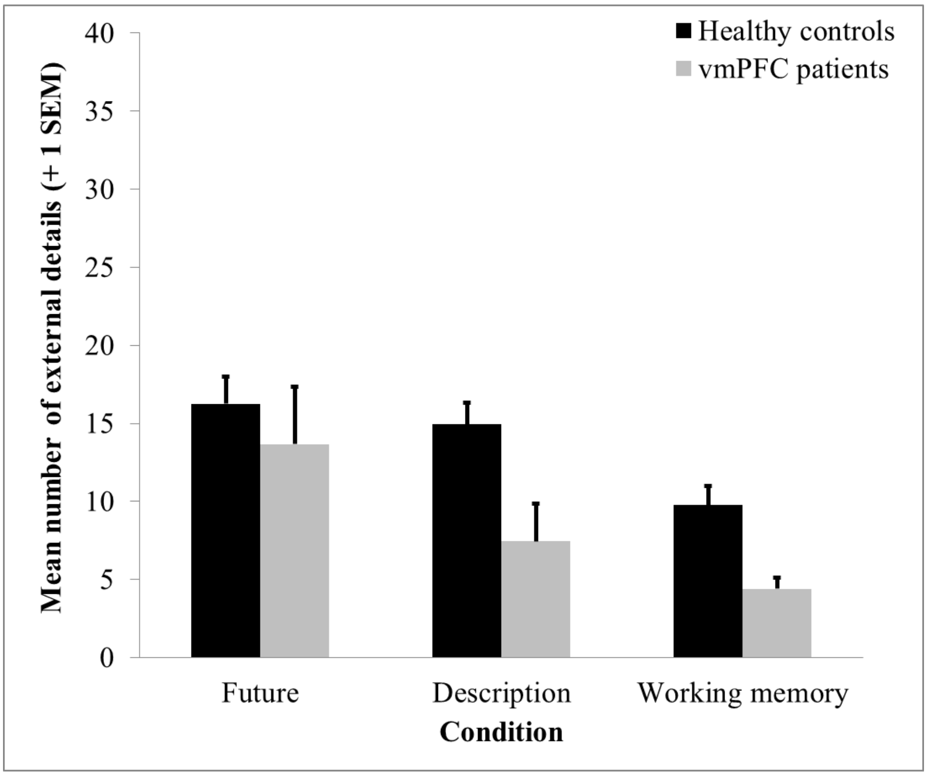

Figure 11. Mean number of external details by participant group and type of condition. Bars represent standard errors of the mean (SEM).

Having established that vmPFC patients produced fewer internal details in all conditions we were interested in understanding if group differences in the future condition remained after controlling for performance in the description and WM conditions. A 2 Group x 2 Detail ANOVA on future condition was run using the number of internal and external details from the description and WM conditions as covariates. Results showed that the interaction Detail x Group was still significant ($F_{(1,11)} = 6.44$, $p = 0.02$): Fisher post-hoc tests revealed that vmPFC patients provided fewer internal details compared to healthy controls (4.28 vs. 19.12, $p = 0.0004$) and no significant differences emerged between groups in external details ($p = 0.47$). The effects of covariates were not significant. Therefore, vmPFC patients' difficulties at imagining future events do not fully depend on poor abilities to describe a scenario or to maintain it in working memory.

In order to account for possible differences in the length of narratives, we ran an additional analysis on the proportions of internal details to the total number of details (total = internal + external details) (see Figure 12). A 2 Group x 3 Condition ANOVA on the proportions of internal to total details indicated a main effect of Condition ($F_{(2,30)} = 46.05$, $p < 0.000001$) qualified by a Group x Condition interaction ($F_{(2,30)} = 10.52$, $p = 0.0003$): a Fisher post-hoc test showed that vmPFC patients produced a smaller proportion of internal to overall details compared to healthy controls in the future condition (0.23 vs. 0.53, $p = 0.00002$) and no differences between groups were found in the description (0.72 vs. 0.67, $p = 0.37$) or WM conditions (0.74 vs. 0.74, $p = 0.98$). This result indicates that when findings are controlled for the total number of details the vmPFC patients' performance on description and WM conditions was similar to healthy controls' performance. On the other hand, there was a significant difference between groups uniquely for the future condition. This evidence supports again the hypothesis that the prospection difficulty that emerged in vmPFC patients is not fully explained by a working memory or narration loss.

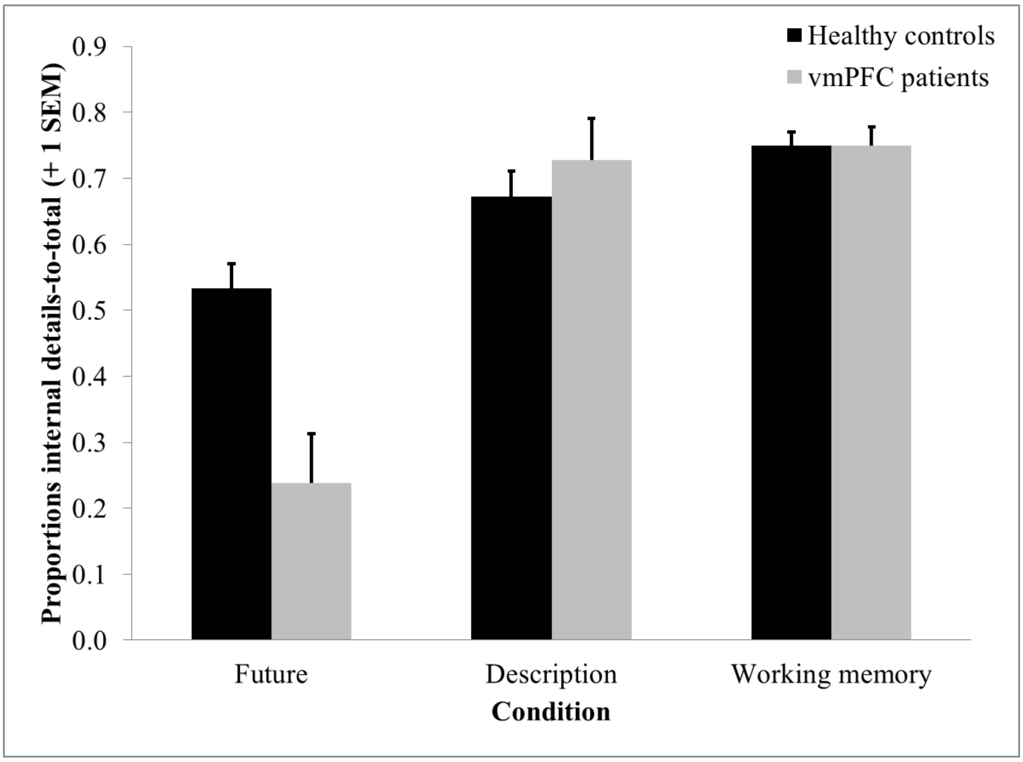

Figure 12. Mean number of proportions internal-to-total number of details by participant group and type of condition. Bars represent standard errors of the mean (SEM).

7.4 Discussion

In the present study we investigate the role that non-episodic abilities, such as narrative abilities and working memory, play in the capacity to construct future episodic experiences in a group of patients with lesions to vmPFC and matched healthy controls. Results confirm that the ability to imagine future experiences was strongly compromised in patients with lesions to the vmPFC compared to healthy controls. Narrative abilities and working memory performance of vmPFC patients were also impaired. However, when controlling for both abilities, evidence for the diminished capability to imagine future episodes in vmPFC patients compared to healthy controls remained, demonstrating that narrative abilities and working memory performance do not fully explain group differences in constructing novel episodic experiences.

In the current study we could replicate results we found in experiments 1 and 2. Specifically, the current pattern of results on EFT is similar to the pattern that emerged in experiment 1: in both cases vmPFC patients produced fewer internal details than healthy controls while imagining personal future episodes but a similar number of external details (note that the same autobiographical interview scoring was employed in both experiments; Levine et al., 2002), indicating a selective impairment of the episodic system. Again, as we showed in experiment 1, poor performance in vmPFC patients in imagining the future is unlikely to be due to a general problem in detail generation because vmPFC patients provided a similar amount of external details as those provided by healthy controls (see also Discussion of experiment 2).

These findings show that vmPFC patients have difficulty in imagining episodic future events consistently across different experimental paradigms: in experiment 1 cue words were employed to remember and imagine different experiences, whereas in the current experiment pictures were used as cues. This diverse modality could have produced different effects on EFT (Williams et al., 1999; Goddard et al., 2005), for example, pictures could have facilitate performance eliciting more details during imagining future events than using words. However, the results are consistent across cueing modality, reinforcing the finding that vmPFC damage disrupts the ability to construct specific future episodes.

Considering previous studies, narrative abilities in describing scenes were intact in patients with amnesia (Race et al., 2011, 2013). However, in a study with a similar task, patients with amnesia showed an impaired performance in describing pictures

(Zeman et al., 2013). Race and colleagues (2013) hypothesized that a diminished narrative capacity in patients included in Zeman et al. (2013)'s study can be caused by brain damage extending beyond the MTL. Our findings are in line with Race et al.'s hypothesis suggesting that a brain lesion, not necessarily in the MTL, may be associated with weak performance in a picture description task. As we mentioned before, performance on a picture description task was found compromised also in aged-participants (Gaesser et al., 2011; Schacter et al., 2013), who often show frontal lobe atrophy (e.g., Raz et al., 2005). However, Gaesser et al. (2011) showed that a residual deficit in EFT related to age survived even after controlling for performance in picture description, similar to what we found in vmPFC patients. Consistently, when participants' performance in the present study was considered in terms of quality, using internal-to-total details ratios, a damage to vmPFC was found to provoke a qualitative disruption of EFT, whereas a preserved quality of narrative and working memory abilities emerged.

In a recent fMRI study, Zeidman and colleagues employed a very similar task to investigate the involvement of the hippocampus in constructing, describing, and maintaining scenes (Zeidman et al., 2015). They observed the involvement of the hippocampus in both perceiving and constructing scenes, but not in maintaining scenes in mind. A possible explanation is that other brain areas are involved in the scene maintenance, for example frontal regions. Recent experimental evidence showed the involvement of the vmPFC in a working memory task (Luu et al., 2014). Consistently, our results suggest that vmPFC may be critical for supporting working memory. We believe that the WM condition in the current study engages processes similarly to the SWM (Meyer and Lieberman, 2012; Meyer et al., 2015). SWM is a kind of working memory specialized for social information and it involves processes similar to mentalizing, in that individuals access, maintain, and work with information concerning the self or others (Meyer and Lieberman, 2012). Similar processes occur during the WM condition in the current task, because participants have to observe a complex scene depicting people doing different activities, have to maintain the scene in mind, and manipulate (work with) the information in memory in order to describe the picture. In accordance with this hypothesis, it has been found that SWM is associated with activation in a network of areas partially overlapping with that involved in mentalizing, including dMPFC, precuneus/posterior cingulate cortex, tempoparietal junction, and the vmPFC (Meyer et al., 2015). That said, our results support a role of vmPFC in EFT above and beyond that played in SWM.

An alternative possible explanation for the few internal details produced by vmPFC patients in both description and WM conditions is a visual search impairment (Adolphs, 2014; Wolf et al., 2014). Previous study demonstrated the engagement of vmPFC together with lateral occipital cortex in visual search tasks (Peelen and Kastner, 2011; Pantazatos et al., 2012). For example, in the study by Pantazatos and colleagues (2012) participants were instructed to indicate the presence and location of a specific object that varied in the size and location in a complex natural visual scene. Findings showed a positive functional connectivity between vmPFC and the lateral occipital cortex during the search task. Both description and WM conditions require visual search in order to detect and describe details. Hence, vmPFC damage may cause an impairment in visual search, and, in turn, poor performance in both the description and WM condition. Further investigation is needed to verify this possibility. Again, this does not fully explain vmPFC patients' deficit in EFT.

To conclude, this experiment shows that vmPFC patients can show poor narrative and working memory abilities, but their deficits do not fully explain vmPFC patients' poor EFT. The results confirm that vmPFC is critical for constructing experiences alternative to the present and pre-experience possible future situations.

8 Experiment 4 - Reduced mind wandering following ventromedial prefrontal damage

8.1 Introduction

Mind wandering occurs when attention shifts away from an ongoing task, or events in the external environment, towards self-generated thoughts that are often completely unrelated to the current perceptual experience, and focused instead on current goals and concerns, memories, and plans for the future (Antrobus et al., 1966; Smallwood and Schooler, 2015; Maillet and Schacter, 2016). Common examples are planning the next vacation in Greece while washing the dishes, or replaying mentally your last meeting with a friend while attending a class (see 3.1).

Given the pervasiveness of the experience of mind wandering and its important psychological function (see 3.1.2), much research is being devoted to reveal its neural and cognitive bases. fMRI evidence indicates that mind wandering is associated with activation of the DMN whose activity is enhanced during relatively passive states (e.g., rest) as compared to most goal-directed tasks, and by internally focused thought (Binder et al., 1999; Mason et al., 2007; Buckner et al., 2008; Christoff et al., 2009; Wang et al., 2009; Stawarczyk et al., 2011). Mind wandering is also associated with activity in regions of the ‘executive network’, including the right dorsolateral prefrontal cortex, left ventrolateral prefrontal cortex, and the anterior cingulate cortex (Christoff et al., 2009; for a meta-analysis see Fox et al., 2015). Activity in the DMN and the executive network is positively correlated during mind wandering, suggesting these networks govern different, complementary component processes of mind wandering (Christoff, 2012; see also Smallwood et al., 2012). Activity in the DMN has been linked to the production of the mental content that commonly populates mind wandering episodes, which generally consists of remembered or simulated experiences involving the self and others (Smallwood and Schooler, 2015). Consistently, remembering the past, envisioning the future, and conceiving the thoughts of other people all activate multiple regions within the DMN (Buckner and Carroll, 2007; Schacter et al., 2012). The executive network may mediate additional processes related to mind wandering, such as working memory and cognitive control (Smallwood and Schooler, 2015; Maillet and Schacter, 2016).

Although fMRI studies have detected activity in the DMN during mind wandering, it is not clear whether activity in different nodes of this network is crucial for the emergence of mind wandering. Here, we focus on the vmPFC. There are several reasons to suspect that vmPFC is a crucial neural substrate of mind wandering. vmPFC is a core component of the DMN (Andrews-Hanna et al., 2010b; Spreng and Grady, 2010), and it is consistently engaged in association with mind wandering (Mason et al., 2007; Christoff et al., 2009; Fox et al., 2015). Moreover, the thickness of mPFC and anterior/midcingulate cortex is positively related to individuals’ tendency to engage in mind wandering under low-demanding conditions (Bernhardt et al., 2014). Consistently, patients with prefrontal cortex lesions are anecdotally reported as not interested or unable to daydream and introspect (Ackerly and Benton, 1948; Wheeler et al., 1997), ‘stimulus bound’ (Knight et al., 1995), and ‘stuck in the present moment’ (Ingvar, 1985). More recent research has shown that patients with lesion to vmPFC are impaired at remembering past events and constructing future events (see Experiments 1 and 2), make “shortsighted” choices during decision-making (Bechara et al., 1994; see also Knight and Grabowecky, 1995), and exhibit steep TD of future rewards (Sellitto et al., 2010), suggesting that these patients may have difficulties at conceiving or constructing scenarios alternative to the immediate environment.

To test whether vmPFC is necessary for mind wandering, we investigated the intensity and quality of mind wandering in vmPFC patients, control patients with lesions outside the vmPFC, and healthy controls. Participants performed three tasks varying in their demands on controlled processes, and were presented with periodic thought probes prompting them to report whether their current thoughts pertained to the task being performed/here and now, or their minds had, to some extent, wandered away from it (mind wandering). As an additional index of the proclivity to engage in spontaneous (as opposed to goal-directed) forms of thought, we assessed participants’ self-reported tendency to daydream, a phenomenon related to (yet not coincident with) mind wandering. Based on fMRI evidence that vmPFC activity is associated with mind wandering (Fox et al., 2015), we predicted that vmPFC patients would exhibit a reduction in mind wandering compared to healthy controls and control patients with brain lesions not involving vmPFC.

8.2 Methods

8.2.1 Participants

Participants included 18 patients with brain damage and 20 healthy individuals (see Table 10 for demographic information). Patients were recruited at the Centre for Studies and Research in Cognitive Neuroscience, Cesena, Italy. Patients were selected on the basis of the location of their lesion evident on MRI or CT scans. Seven patients had lesions involving the vmPFC (vmPFC patients). Lesions were the results of the rupture of an aneurysm of the ACoA in all cases. Lesions were bilateral in all cases, though often asymmetrically so (see Figure 13). Eleven patients were selected on the basis of having damage that did not involve the vmPFC (control patients). In this group, lesions were unilateral in 9 cases (four in the left hemisphere, and five in the right hemisphere), and bilateral in 2 cases, and were all caused by ischemic or hemorrhagic stroke. Lesion sites mainly included the occipital cortex (7 cases), and extended, in a few cases, to the lateral fronto-parietal cortex (2 cases), and the cerebellum (2 cases). Included patients were tested at least 3 months after the brain insult, 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 or alcohol abuse). There was no significant difference in lesion volume between vmPFC patients and control patients (58.79 vs. 33.66 cc, t test: $t = 1.61$; $p = 0.13$). Note that in one vmPFC patient artifacts induced by a metallic clip made it impossible to identify precisely the extension of the (small) lesion (see below).

The healthy control group comprised 20 individuals matched to patients on mean age and education. ANOVA with Group (vmPFC patients, control patients, healthy controls) as factor confirmed no group differences in age ($F_{(2,35)} = 0.33$, $p = 0.72$) or education ($F_{(2,35)} = 0.27$, $p = 0.77$). 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, 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).

8.2.1.1 Cognitive profile

Patients' general cognitive functioning was generally preserved, as indicated by the scores they obtained in the Raven Standard Matrices (RMS), the phonemic fluency test (PF), and the digit span test (DS), which were within the normal range in all cases, and similar between patient groups (t test: $t < 0.83$, $p > 0.41$ in all cases). All groups were also evaluated on working memory and cognitive flexibility, two aspects of executive functioning that may have an impact on mind wandering and be impaired following prefrontal cortex lesions (Baldo & Shimamura, 2002; DeLuca & Diamond, 1995; Mesulam, 2002; Shallice, 1982; Stuss & Benson, 1984). Working memory was assessed with a 2-back task (based on Zimmermann & Fimm, 2002), requiring to monitor a series of numbers, and signal whether the number currently presented matched the number presented two trials back (1 control patient was no longer available for testing). Cognitive flexibility was assessed with the Weigl Color-Form Sorting Test (Weigl, 1927), which requires classifying a series of stimuli according to different criteria, for example shape, color, and size, and switch to a different classification criterion upon request (2 control patients and 2 healthy controls were no longer available for testing). Group differences in accuracy in the 2-back task did not reach conventional levels of statistical significance ($F_{(2,34)} = 2.76$, $p = 0.08$), although vmPFC patients’ performance ($M = 0.52$) tended to be weaker than control patients’ ($M = 0.66$)

and healthy controls' (M = 0.80). As well, there was a marginally significant difference in the WCFT accuracy score (highest possible score = 15; Weigl, 1927) across groups ($F_{(2,31)}$ = 3.14, p = 0.06): vmPFC patients' performance (M = 8.43) tended to be weaker than control patients' (M = 11.56) and healthy controls' (M = 11.50).

vmPFC patients also received a more extensive neuropsychological battery, aimed at qualifying their cognitive profile further. This revealed normal performance in standard tests of executive functioning, such as the Tower of London test (t-score = 43.57; cut off = 30) (Culbertson and Zillmer, 2000), phonemic fluency (mean equivalent score (ES) = 2.29. Note that the equivalent score ranges from 0 = impaired performance, and 1 = borderline performance, to 2 - 4 indicating normal performance), semantic fluency (ES = 3), and the Stroop test (mean number of errors = 0.79, cut off > 7.5) (Spinnler and Tognoni, 1987). Verbal short-term memory (Digit span; ES = 3.14) and spatial short-term memory (Corsi test; ES = 3) (Spinnler and Tognoni, 1987) were also preserved. Long-term memory was weak, but within the normal limits, as assessed with the Buschke–Fuld list-learning Test (Buschke & Fuld, 1974; Long Term Retrieval ES = 1.57) and a prose-passage recall test (ES = 1.86) (Spinnler and Tognoni, 1987). In previous studies, however, we have shown that vmPFC patients (including a subset of patients described here) have impaired episodic memory and future thinking (Bertossi et al., 2016a, 2016b; see also Moscovitch and Melo, 1997; Levine, 2004). More recently, 6 of the 7 vmPFC patients involved in the present study also participated in an experiment requiring to imagine personal future events using pictures as cues (see Experiment 3). The results confirm that vmPFC patients are impaired in imagining specific personal future events compared to healthy controls, producing fewer internal (episodic) details

(4.28 vs. 19.12, Mann-Whitney test: z = -3.17, p = 0.0003) but a similar number of external (semantic) details (13.67 vs. 16.24, z = -1.05, p = 0.30).

Table 10. Participants' demographic and clinical information

Group	N	Age (Years)	Education (Years)	Sex	2-back (Accuracy)	SRM	PF	DS
vmPFC patients	7	56.00(3.01)	11.71(1.21)	6 M; 1 F	0.52(0.12)	34.29(3.14)	26.57(2.29)	5.57(3.14)
CP	11	55.36(3.20)	10.64(1.30)	10 M; 1 F	0.66(0.10)*	32.9(3.50)	33.12(2.75)	5.62(3.50)
HC	20	52.85(2.53)	11.50(0.69)	20 M	0.80(0.05)	-	-	-

Note. vmPFC = ventromedial prefrontal cortex; CP = control patients; HC = healthy controls; M = male; F = female; SRM = Standard Raven Matrices; PF = phonemic fluency; DS = digit span. For SRM, PF, and DS, we report the mean uncorrected scores and, in brackets, the mean equivalent score (with 0 = pathological performance, 1 = borderline performance, 2 – 4 = normal performance). For age and education, the values in brackets are standard errors of the mean. * Results based on 10 control patients.

8.2.2 Lesion analysis

Patients' individual lesions, derived from the most recent magnetic resonance imaging (MRI; N = 12) or computerized tomography (CT; N = 5) images, were manually drawn by an expert neurologist (not involved in the present study, and blind to task performance), or by E.B., and then verified by the same neurologist, directly on each slice of the normalized T1-weighted template MRI scan from the Montreal Neurological Institute (Rorden and Brett, 2000). This template is approximately oriented to match Talairach space (Talairach and Tournoux, 1988) and is distributed with MRIcro (Rorden and 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. As anticipated, for one patient artifacts due to the presence of a metallic clip made it impossible to reconstruct precisely the extension of the lesion. The lesion appeared relatively small, and located in the ventral part of vmPFC, in line with the etiology (ACoA aneurysm). We, therefore, included the patient in our vmPFC sample (the results do not change if we excluded this patient from the analyses).

Figure 13 shows the extent and overlap of brain lesions in the remaining 6 vmPFC patients. Brodmann's areas (BA) affected were areas BA 10, BA 11, BA 24, BA 25, BA 32, BA 46, BA 47, 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).

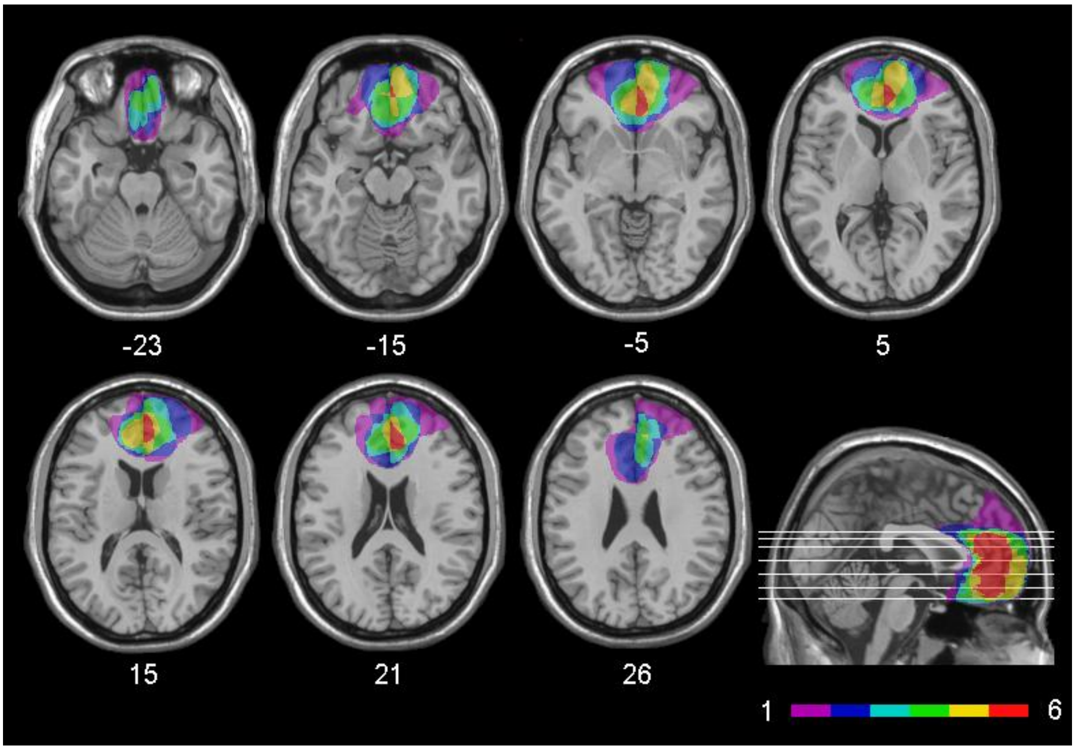

Figure 13. Extent and overlap of brain lesions. The figure represents vmPFC patients' lesions projected on the same six axial slices and on the sagittal view of the standard Montreal Neurological Institute brain. The white horizontal lines on the sagittal view are the positions of the axial slices, and 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 BA 10, 11, and 32. The left hemisphere is on the left side.

8.2.3 Mind wandering assessment

Participants underwent three computerized tasks varying in cognitive demands and conduciveness to mind wandering: a working memory task (WM), a choice reaction time task (CRT), and a "Passive" task, modified from previous studies (Smallwood et al., 2009, 2011b). The WM task required monitoring a series of digits (1-8), presented in black ink and appearing in the center of the screen (non-target stimuli). Non-target stimuli presentation rate was 1 item every 1500 ms (followed by a 2000 ms fixation cross). Interspersed with the digit presentation were question marks presented in green ink (target stimuli), appearing for 2000 ms. The appearance of a green question mark cued participants to report whether the previous digit was even or odd using one of two keys. In the CRT task, individuals saw a similar stream of digits (from 1-8), written in a black ink and appearing in the center of the screen (non-target stimuli). This time, target stimuli were digits presented in green ink, which cued participants to report whether the currently presented number was even or odd. In both tasks, a total of 156 non-targets and 25 targets were presented. Non-target and target stimuli were arranged in five blocks containing approximately 5 targets and 31 non-targets each, so to have target stimuli distributed over the course of the task. The order of the five blocks was randomized for each participant. In the Passive task, participants were told to merely observe a series of 180 digits (from 1-8), written in a black ink and appearing in the center of the screen. Similar to the WM and CRT tasks, presentation rate in the "Passive" task was 1 item every 1500 ms (with a 2000 ms fixation cross), and the stimuli were arranged into 5 blocks, whose order was randomized for each participant.

Mind wandering was assessed through the presentation of 5 "thought probes", one for each block, during each of the three tasks. Thought probes were presented visually on the computer screen. Firstly, participants were required to rate on a 7-point Likert scale the degree to which their current thoughts were on-task, i.e., focused on the task being performed, or off-task, i.e., pertaining to something different (from 1 – completely on-task, to 7 – completely off-task; see below). If participants provided an answer from 2 to 7, meaning they were, to some extent, off-task, they then classified their thoughts in one of 5 categories: 1) Past (i.e., the thought pertained to the past; e.g. "My latest trip to Rome was the best"); 2) Present (i.e., the thought pertained to the present; e.g. "I wonder what my wife is doing now"); 3) Future (i.e., the thought pertained to the future; e.g. “Next week I will go to the dentist”); 4) Time not clear (i.e., the thought was not easily classified into time categories, e.g. “I’m lucky to have a friend like him”); 5) Unaware (i.e., the participant is not aware of the contents of her/his thoughts). Participants then specified whether their thoughts were 1) Self-related (i.e., the thought mainly pertained to the self; e.g. “I am going to bed after this”), 2) Other-related (i.e., the thought mainly pertained to other people; e.g. “My son is growing up so fast”), or 3) Unrelated to people (i.e., the thought did not involve people; e.g. “The new car was a good deal”). The three tasks were administered in 3 different testing sessions, each lasting approximately 12 minutes, in a counterbalanced order. The 3 testing sessions took place, in general, on different days. Five patients (4 control patients and 1 vmPFC patient), who were unavailable to come to the lab three times, performed 2 tasks the same day, with a 30-minute break in between.

Our experimental procedures rest on the assumption that patients understood the distinction between on-task and off-task thought, and were able to classify occurring thoughts based on that distinction. To make sure this was indeed the case, we adopted several measures. First, before the start of the first testing session, patients were familiarized with the concept of mind wandering, off-task thought and on-task thought. We told them that individuals’ thoughts may occasionally depart from current activities, and focus instead on something unrelated to the task at hand. We paid attention not to give either a positive or negative connotation of mind wandering to avoid social desirability biases. We provided an example of mind wandering: mentally planning the next vacation while washing the dishes. We told them that thoughts deviating from the task at hand were to be considered off-task (next vacation), whereas thoughts focused on the current activity (washing dishes) were to be considered on-task. All participants, including vmPFC patients, immediately related to the concept of mind wandering, and could provide additional examples on their own. The distinction between on-task and off-task was reiterated in the context of the WM, CRT, and "Passive" tasks. Participants were instructed to classify as "on-task" thoughts strictly related to the execution of the computerized tasks, focusing on the stimuli and task procedures (e.g., "5 is odd, so I am pushing this button!"), and to classify as "off-task" thoughts that were irrelevant to the task being performed (e.g., "I need to see the dentist later"). All participants understood the instructions and could recall them back to the experimenter.

As an additional check, at the end of the experiment we had a subset of vmPFC patients and healthy controls classify another person's thoughts as on-task or off-task. In the context of a pilot experiment using the CRT task, participants reported the content of thoughts they had classified as on-task or off-task. We chose 20 such thoughts, of which 5 on-task (e.g., "5! So that's odd") and 15 off-task. The 15 off-task thoughts comprised 5 past-related thoughts (e.g., "When we purchased that washing machine we made a big mistake"), 5 present-related thoughts (e.g., "I'm wondering what my son is doing right now"), and 5 future-related thoughts (e.g., "Next week beach for sure"). Five vmPFC patients and twelve healthy controls were presented with the 20 thoughts in a randomized order. They were told that another (hypothetical) individual, Mario, had performed a task requiring to monitor black and green digits on a computer screen, and classify green digits as even or odd. At the end of the task, Mario had reported 20 thoughts that had popped into his mind while doing the task, and we now wanted their opinion as to whether they would consider each thought as on-task or off-task. We found no significant difference in classification accuracy (on-task/off-task) between vmPFC patients and healthy controls (0.96 vs. 0.91, $t = -0.88$, $p = 0.39$), suggesting vmPFC patients could comply with task instructions.

8.2.4 Imaginal Processes Inventory

Participants completed the daydreaming and night dreaming frequency scales of the Imaginal Processes Inventory (IPI, Singer and Antrobus, 1972), a questionnaire designed to examine individual differences in inner mental life. In a series of 12 daydreaming and 12 night dreaming items, individuals rated the frequency with which they experienced daydreaming in their daily life (i.e., Daydreaming frequency scale: e.g., “Whenever I have time on my hand I daydream”, from 1 – Never to 5 – Always), and night dreaming (i.e., Night dreaming frequency scale; e.g., “A night’s sleep for me contains a dream”, from 1 – Rarely or never to 5 – Once a night). In each scale, the score ranges from 12 to 60, with higher scores indicating a higher propensity toward daydreaming and night dreaming.

8.3 Results

8.3.1 WM and CRT: accuracy and reaction times

Table 11 portrays accuracy (number of correct odd/even responses) and reaction times (RTs) data by Group (vmPFC patients, control patients, and healthy controls) and Task (CRT, WM). A Group x Task ANOVA on the number of correct responses showed no significant main effect or interaction ($p > 0.45$ in all cases). The same ANOVA on RTs for correct responses revealed a main effect of Group ($F_{(2,35)} = 5.04$, $p = 0.01$), which was qualified by a significant Group x Task interaction ($F_{(2,35)} = 3.38$, $p = 0.04$). Newman-Keuls post-hoc tests showed that in the WM task vmPFC patients were slower than healthy controls (1321 vs. 883 ms, $p = 0.005$) and control patients (1321 vs. 1007 ms, $p = 0.04$), whereas no difference emerged between control patients and healthy controls ($p = 0.53$). Group differences in RTs in the CRT task were not significant ($p > 0.21$). Thus, vmPFC patients had a weaker working-memory performance than the control groups, in line with the results in the 2-back task.

Table 11. Accuracy and reaction times of CRT and WM tasks

	CRT		WM	
Group	Accuracy	RT	Accuracy	RT
vmPFC patients	23.29(0.68)	1147.44(106.81)	23.00(0.53)	1321.11(106.59)
CP	23.27(0.88)	1070.67(78.55)	22.27(1.06)	1006.64(92.00)
HC	23.55(0.65)	921.06(47.58)	23.60(0.56)	883.03(61.17)

Note. vmPFC = ventromedial prefrontal cortex; CP = control patients; HC = healthy controls; CRT = Choice reaction times; WM = Working Memory; RT = Reaction Times for correct responses. In parenthesis: the standard errors of the mean.

8.3.2 Mind wandering

8.3.2.1 Intensity

As Figure 14 illustrates, the reported intensity of mind wandering was lower for vmPFC patients than both control groups across tasks. An ANOVA on mean mind wandering ratings with Group as between-subject factor and Task (WM, CRT, Passive) as within-subject factor showed a main effect of Group ($F_{(2,35)} = 6.74$, $p = 0.003$): vmPFC patients evinced lower mind wandering ratings than healthy controls (1.33 vs. 3.17, $p= 0.002$) and control patients (1.33 vs. 2.59, $p = 0.02$), whereas no significant difference emerged between healthy controls and control patients ($p = 0.25$). Group differences on mind wandering were confirmed using more robust, non-parametric Mann-Whitney tests: vmPFC patients mind-wandered less than healthy controls (CRT task: $z = 3.50$, $p = 0.0001$; WM task: $z = 3.55$, $p = 0.0001$; “passive” task: $z = 2.86$, $p = 0.003$) and control patients (CRT task: $z = 2.99$, $p = 0.002$; WM task: $z = 2.53$, $p = 0.03$; “passive” task: $z = 2.42$, $p = 0.02$), whereas no significant differences emerged between control groups (p values > 0.09). The ANOVA also revealed a significant effect of Task ($F_{(2,70)} = 28.74$, $p < 0.000001$), such that all participants mind-wandered more in the Passive task than in the CRT task (3.59 vs. 2.43, $p = 0.0001$), and mind-wandered more in the CRT task than in the WM task (2.43 vs. 1.97, $p = 0.01$). Several studies have shown that mind wandering is modulated by the complexity of the ongoing task, and it tends to be less frequent when the external task is more difficult (Teasdale et al., 1993; Kane et al., 2007; Smallwood et al., 2009, 2011b; Levinson et al., 2012). We observed this normal modulation of mind wandering in all groups, including vmPFC patients. This result suggests that patients complied with task instructions.

This first set of analyses confirms that vmPFC patients experience mind wandering less frequently than healthy and brain-damaged controls. We note that 4 vmPFC patients never reported mind wandering. Even patients who did report mind wandering, however, evinced lower intensity ratings (collapsed across the CRT, WM, and “passive” tasks) than healthy controls (1.17 vs. 3.17, Mann-Whitney test: $z = 2$, $p = 0.04$). We asked the vmPFC patients who never reported mind wandering whether mind wandering had occurred far from the thought probes, and therefore had not been recorded. They stated confidently that mind wandering had never occurred. We also asked a vmPFC patient, G.V., to describe what exactly was in his mind while being on-task in the “Passive” task. He said: “I just look at the numbers, inspect them, examine their shape”, confirming a tendency to stick to external stimuli, as opposed to mind-wander toward internal information.

Because there was a significant difference in RTs in the WM task between vmPFC patients and controls, we ran again the ANOVA on mind wandering ratings adding RTs in the WM task as a covariate. The effect of the covariate was significant ($F_{(1,34)} = 5.63$, $\beta = 0.34$ $p = 0.02$) such that, in general, a strong tendency to mind-wander was associated with a slow performance in the ongoing WM task. The effect of Group remained significant ($F_{(2,34)} = 10.45$; $p = 0.0003$), with vmPFC patients showing less mind wandering than both healthy ($p = 0.001$) and control patients ($p = 0.01$), and no difference between the control groups ($p = 0.22$). The effect of Group in the ANCOVA remained significant also if we added accuracy in the 2-back task and the Weigl Color-Form Sorting Test as two additional covariates ($F_{(2,28)} = 7.42$; $p = 0.003$), with vmPFC patients exhibiting less mind wandering than healthy ($p = 0.002$) and brain-damaged controls ($p = 0.04$), and no difference between the control groups ($p = 0.12$). The effect of the covariates was not statistically significant ($p > 0.053$ in both cases). These findings suggest that vmPFC patients’ problems in working memory and cognitive flexibility do not significantly explain their abnormally low tendency towards mind wandering.

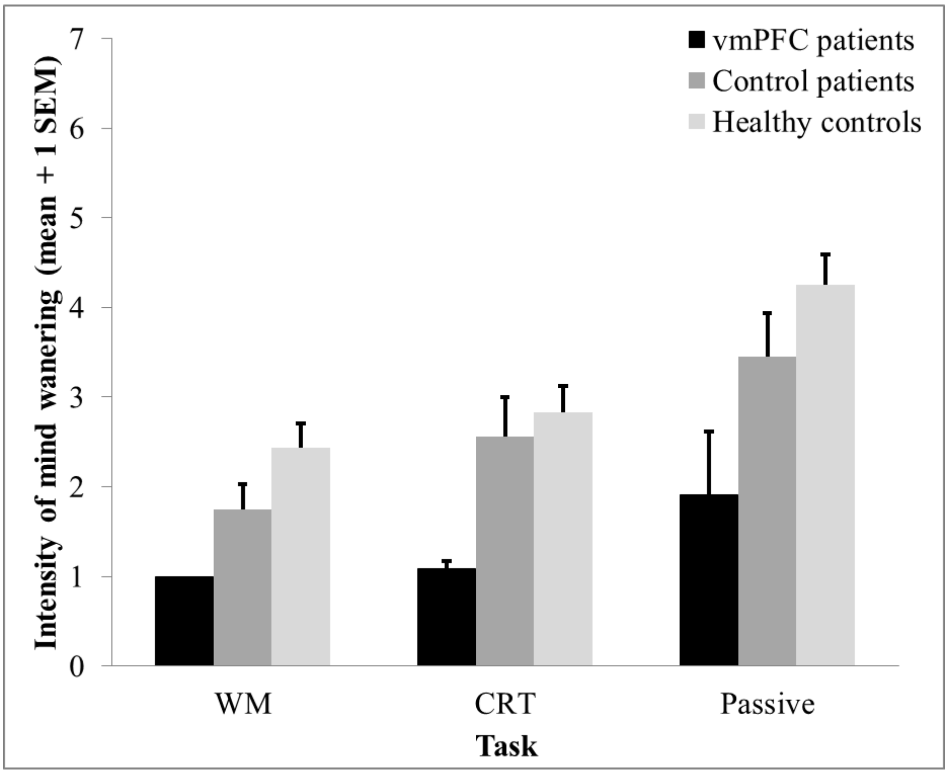

Figure 14. Intensity of mind wandering by participant group and type of task (WM, CRT, “Passive” tasks). Bars represent standard errors of the mean (SEM).

8.3.2.2 Intensity of mind wandering and cognitive profile: exploratory analyses

Given that mind wandering ratings varied in vmPFC patients, we explored whether these correlated with several aspects of vmPFC patients’ neuropsychological profile, running non-parametric Spearman correlation analyses. We found that mind wandering ratings (collapsed across the CRT, WM; and Passive task, but similar results were obtained considering the 3 tests separately) did not correlate with vmPFC patients’ scores in short-term and long term memory (digit span test, Corsi test, Buschke-Fuld task, prose-passage recall task), non verbal reasoning (Raven Standard Matrices), verbal fluency and executive functioning (verbal fluency, Tower of London task, Stroop task) ($p > 0.19$ in all cases). However, mind wandering ratings correlated with the number of details (collapsed across internal and external details) produced while imagining personal future events (r = 0.88, p = 0.02).

8.3.2.3 Content of mind wandering

We also investigated whether, beyond decreasing the tendency to mind-wander, vmPFC damage altered the content of mind wandering episodes. We counted the number of times participants described the contents of their thoughts (collapsing across the WM, CRT, and "Passive" tasks, but conceptually similar results were obtained considering the 3 tasks separately) as belonging to different content categories (Past, Present, Future, Time not clear, Self-related, Other-related, Unrelated to people, Unaware), and compared the obtained values across groups using non-parametric tests (data were, in most cases, non-normally distributed).

As Table 12 shows, vmPFC patients tended to show fewer instances of mind wandering across content categories, and, notably, they never reported future-related thoughts. Kruskal-Wallis one-way ANOVAs run on each content category separately, however, revealed statistically significant group differences only for the Future category (χ^2 = 8.81, p = 0.01) and Past category (χ^2 = 7.48; p = 0.02). Post hoc comparisons, run with the Mann–Whitney's test, revealed that vmPFC patients experienced fewer future-related thoughts than healthy controls (0 vs. 2.85, z = 3.22, p = 0.001) and control patients (0 vs. 1.45, z = 2.80, p = 0.008), whereas no difference emerged between control patients and healthy controls (p = 0.14). Analogously, vmPFC patients experienced fewer past-related thoughts than healthy controls (0.14 vs. 1.65, z = 2.57, p = 0.01) and control patients (0.14 vs. 1.91, z = 2.53, p = 0.01), while no difference emerged between the control groups (p = 0.64). The deficit in producing future-related mind wandering emerged even if we restricted our analyses to vmPFC patients who did experience mind wandering (vmPFC patients vs. healthy controls: Mann-Whitney z = 2.23, p = 0.02; vmPFC patients vs. control patients: Mann-Whitney z = 1.96, p = 0.049), and even if we compute the proportion of future to total mind wandering episodes (vmPFC patients vs. healthy controls: Mann-Whitney z = 2.22, p = 0.03; vmPFC patients vs. control patients: Mann-Whitney z = 1.94, p = 0.05). This second set of findings suggests that vmPFC damage alters not only the tendency towards mind wandering, but also the content of mind wandering, reducing thoughts that depart from the here and now, and totally abolishing those directed towards the future.

Table 12. Contents of thoughts collapsed across WM, CRT, and "passive" tasks and counted for each content category

Group	Past	Present	Future	Time not clear	Unaware	Self	Other	None
vmPFC patients	0.14(0.14)	1.00(0.58)	0	0.29(0.29)	0	0.57(0.30)	0.57(0.57)	0.29(0.29)
CP	1.91(0.49)	4.00(0.71)	1.45(0.39)	1.45(0.54)	0.27(0.14)	2.36(0.70)	3.91(0.62)	2.54(0.61)
HC	1.65(0.36)	4.70(0.66)	2.85(0.57)	1.50(0.33)	0.35(0.13)	3.25(0.68)	4.75(0.67)	2.70(0.65)

Note. vmPFC = ventromedial prefrontal cortex; CP = control patients; HC = healthy controls; In brackets: the standard errors of the mean.

8.3.3 Night dreaming and daydreaming frequency subscales

An ANOVA on daydreaming frequency scores with Group as a between-subject factor yielded a significant effect of Group ($F_{(2,35)} = 3.53$; p = 0.04). Newman-Keuls post-hoc tests revealed that vmPFC patients reported less frequent daydream than healthy controls (27.14 vs. 37.30, p = 0.02) and control patients (27.14 vs. 37.64, p =

0.03), whereas no differences emerged between the control groups (p = 0.93). The same ANOVA on night dreaming frequency scores revealed no significant effect of Group (p = 0.62). These results indicate a reduced self-report of daydreaming, but not night dreaming, in vmPFC patients (see Figure 15).

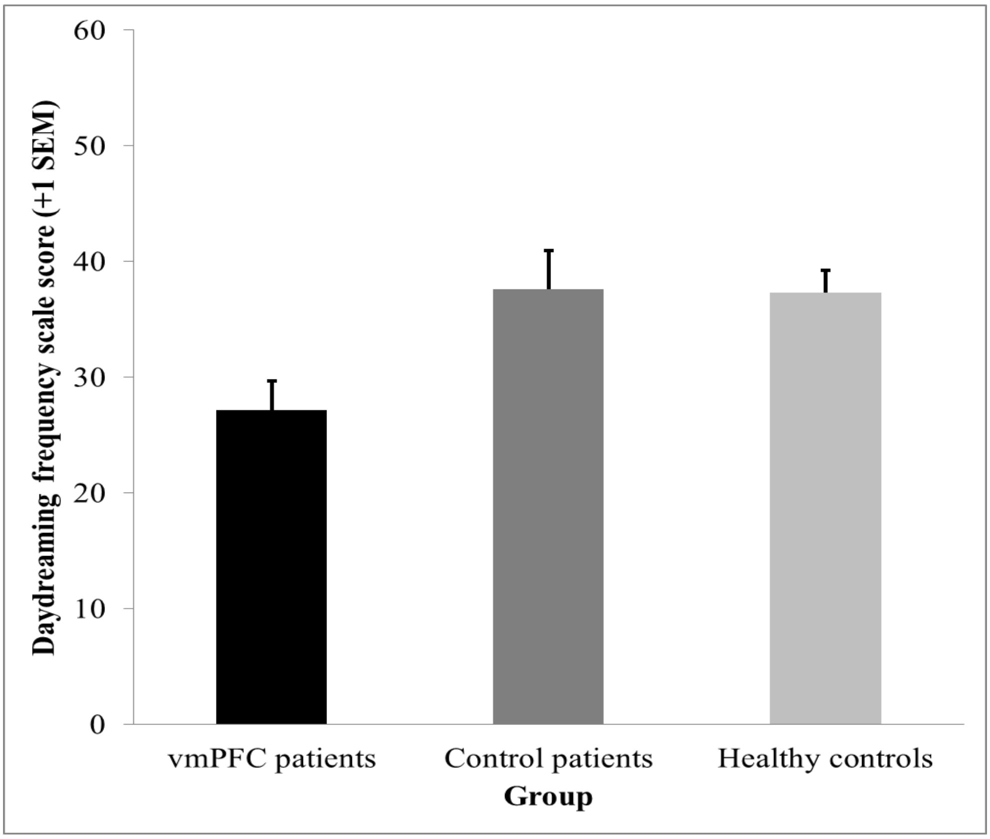

Figure 15. Scores on Daydreaming scale of Imaginal Processes Inventory by participants group. Bars represent standard errors of the mean (SEM).

8.4 Discussion

The present study investigated the neural correlates of mind wandering, an extremely frequent (and likely necessary) expression of humans' mental life that complements goal-oriented, externally-driven forms of cognition. Previous fMRI studies have pointed to the DMN as an important neural substrate of mind wandering, and, in particular, prominent loci of activations have been detected consistently in the vmPFC (Fox et al., 2015). However, fMRI studies are correlational, and cannot establish causal links between brain and behavior. Here, we showed that patients with focal lesions to the vmPFC exhibit a reduced propensity to mind-wander during three experimental tasks, and claim less frequent daydreaming than healthy individuals. Notably, a reduction in spontaneous forms of cognition is not a general consequence of brain damage. Indeed, control patients with lesions mainly affecting the occipital cortex, a region which is not part of the DMN, showed the same tendency to self-report mind wandering and daydreaming than healthy controls. The results are also unlikely to depend on problems in understanding concepts like mind wandering, on-line thought, and off-line thought on the vmPFC patients' part, or a tendency to underreport any type of inner experience. vmPFC patients, indeed, correctly detected instances of mind wandering produced by others, and their tendency to mind-wander, though scant, was related to the demands of the ongoing task, as it was in the control groups. Moreover, they reported similar night dreaming rates than the control groups, suggesting they can, to some extent, introspect on inner experiences.

These findings point to a significant reduction of mind wandering following vmPFC damage, indicating that the vmPFC plays a causal role in mind wandering, in line with fMRI evidence (Binder et al., 1999; Mason et al., 2007; Christoff et al., 2009;

Andrews-Hanna et al., 2010a). We propose two mechanisms by which vmPFC may contribute to the emergence of mind wandering episodes. vmPFC is part of the so called MTL subsystem of the DMN, and is functionally connected with the MTL during construction of mental simulations based on memory (Andrews-Hanna et al., 2010b; see also Benoit and Schacter, 2015). Consistently, vmPFC patients are impaired at remembering personal past events and imagining future events (Bertossi et al., 2016a, 2016b). As anticipated, mind wandering occurs when attention shifts from the external ongoing task towards inner contents. If, however, vmPFC patients have lost the neural machinery needed to construct events alternative to perceptual reality (Bertossi et al., 2016a, 2016b), there would be no internal event capable to overtake the saliency of ongoing external events, resulting in low mind wandering rates. On this view, vmPFC damage would downregulate mind wandering directly, by reducing the 'raw content' mind wandering episodes are made of. An alternative possibility is that vmPFC damage reduced meta-awareness, i.e., one's explicit knowledge of the current contents of thought (Schooler et al., 2011), and, in turn, the frequency with which patients became aware and reported mind wandering episodes, without necessarily affecting the occurrence of mind wandering itself (Smallwood and Schooler, 2015). Anterior and medial regions of prefrontal cortex, damaged in our vmPFC patients, have previously been implicated in meta-awareness of one’s own internal mental contents (Gilbert et al., 2007; Fleming and Dolan, 2012). Moreover, regions implicated in mind wandering, including vmPFC, were found differentially engaged by unaware vs. aware mind wandering (Christoff et al., 2009). It is possible, therefore, that vmPFC damage caused a difficulty in noticing the contents of mind wandering, or the mind wandering process itself. We cannot determine to what extent vmPFC patients' reduced self-report of mind wandering in this study depended on impaired construction or detection of mind wandering, but we favor the first interpretation for a number of reasons. First, vmPFC patients were externally probed to report mind wandering, which minimizes demands on meta-awareness. Moreover, vmPFC damage reduced most dramatically mind wandering episodes focusing on future and past events, consistent with vmPFC's involvement in MTT (Bertossi et al., 2016b), and not those in which participants claimed they were unaware of the contents of mind wandering, as one would have expected in case of a prominent deficit in meta-awareness. Future studies using indirect (e.g., physiological) indices of mind wandering, or sampling both self-caught and probe-caught mind wandering, will be useful to reveal if, and to what extent, lack of meta-awareness contributed to reduced mind wandering in vmPFC patients (e.g., Franklin et al., 2011; Hawkins et al., 2015; Mittner et al., 2014).

A few other studies have tested whether brain regions active during mind wandering during fMRI play a causal role in mind wandering. Axelrod et al. (2015) showed increased propensity to mind-wander following anodal (excitatory) transcranial direct current stimulation (tDCS) over the left dorsolateral prefrontal cortex (dlPFC) (see also Kajimura and Nomura, 2015). Despite using different methodologies, Axelrod et al. (2015)'s study and ours converge in showing that prefrontal cortex regions are crucially implicated in mind wandering. One important question is whether the role played by vmPFC and dlPFC in supporting mind wandering can be differentiated. tDCS has low spatial resolution, and therefore it is not possible to determine with certainty whether the effects observed by Axelrod and colleagues were due specifically to the stimulation of dlPFC, or also of nearby regions such as medial prefrontal and frontopolar cortices. One aspect of Axelrod et al. (2015)'s data, however, suggests that the results were likely to be mediated by dlPFC. In addition to mind wandering, tDCS over dlPFC enhanced, to some extent, performance in the ongoing external task (i.e., the SART; Axelrod et al., 2015), which required sustained attention and cognitive control. The authors reasoned that dlPFC stimulation had increased the capacity of the executive system (Miller and Cohen, 2001), resulting in increased performance as well as mind wandering. There is evidence, indeed, that the executive system supports some components of mind wandering (Teasdale et al., 1993; Smallwood and Schooler, 2006; Smallwood et al., 2009, 2011b; Levinson et al., 2012). Differently, even though our vmPFC patients were mildly impaired in tests of working memory and cognitive flexibility, we have no evidence that patients' low mind wandering ratings were related to poor executive functioning or lack of cognitive resources. First, group differences in mind wandering held after controlling for working memory and cognitive flexibility performance. Moreover, vmPFC patients evinced extremely low mind wandering ratings even in the Passive task, which had minimal cognitive demands, if not at all. Finally, mind wandering ratings did not correlate with any aspect of vmPFC patients executive/cognitive functioning, while they did correlate significantly with the number of details produced while imagining future events, which further reinforces our 'event-construction' account of the role of vmPFC in mind wandering. Interestingly, in Axelrod et al. (2015)'s study, tDCS over a control site in the occipital cortex had no effect on mind wandering, in line with our results of normal mind wandering in control (mainly occipital) patients. These findings reinforce the idea that a reduction of mind wandering is not merely the effect of damage to (or interference on) any brain region, but, more likely, of damage inflicted on a well-delineated system supporting the emergence of mind wandering (Fox et al., 2015), and including the DMN.

The DMN has been thought of as a neural device to escape the here and now (Buckner and Carroll, 2007; Buckner et al., 2008; Schacter et al., 2012). This study provides support to this conceptualization, showing that, even while doing a boring task with minimal demands, vmPFC patients' mind tended to stay focused on the ongoing task, rather than take the chance to wander towards, and explore, possible alternative scenarios. This finding aligns to previous evidence that vmPFC patients are impaired at constructing past and future events voluntarily (Bertossi et al., 2016a, 2016b), suggesting that a deficit in conceiving events alternative to those unfolding in the present can extend from goal-directed to spontaneous cognition, and to evidence that vmPFC patients show steep temporal discounting of future rewards (Sellitto et al., 2010), indicating preference for immediacy during choice. A recent study has demonstrated that cortical thickness in medial prefrontal regions predicts both the proclivity to mind-wander and the ability to resist immediate temptation in a temporal discounting task (Bernhardt et al., 2014). Thus, reduced mind wandering, MTT, event construction, as well as steep temporal discounting are likely to be different expressions of the same underlying deficit in transcending the present and projecting one's self in alternative realities (Buckner and Carroll, 2007; Buckner et al., 2008; Hassabis and Maguire, 2009; Schacter et al., 2012).

To conclude, we have shown that vmPFC patients report significantly fewer mind wandering episodes than healthy as well as brain-damaged controls, indicating that vmPFC plays a crucial role in mind wandering, possibly by mediating construction of events alternative to the here and now. Future studies will be needed to specify the precise nature of the contribution of vmPFC, as well as other nodes of the DMN, to mind wandering. For the time being, we have shown that vmPFC patients' conscious experience is abnormally bound to the external, perceptual reality, which deprives vmPFC patients of the possibility to conceive, foresee, and 'visit' alternative scenarios, and, more generally, to integrate external with internal experiences while constructing (understanding) their own reality.

9 Experiment 5: Transcranial direct current stimulation of the medial prefrontal cortex modulates mind wandering

9.1 Introduction

In Experiment 4, we found that patients with damage to the vmPFC showed reduced intensity of mind wandering. Indeed, vmPFC patients' propensity to mind-wander was diminished relative to patients with lesions to posterior brain regions (control patients), and healthy controls, while control patients and healthy participants had a similar propensity for mind wandering. These findings, in line with previous neuroimaging results (e.g., Mason et al., 2007; Christoff et al., 2009), showed a specific role of vmPFC in spontaneous cognition. The current study is aimed to replicate our previous experimental findings using tDCS in healthy individuals. tDCS involves continuous administration of weak currents through the skull using a pair of electrodes. tDCS modifies spontaneous neuronal excitability hyperpolarizing neurons (e.g., Nitsche et al., 2008) and several studies have shown that cathodal tDCS reduces cortical excitability in the targeted brain regions (Nitsche et al., 2003; Nitsche and Paulus, 2011).

The main goal of this study is to investigate whether the modulation of cortical excitability of the mPFC affects the intensity of mind wandering in a group of healthy young participants. Considering results derived from experiment 4, we predicted that an inhibitory effect of cathodal tDCS over the mPFC would decrease mind wandering, whereas, a similar modulation of activity in a control (occipital) region would have no effect on mind wandering.

Modulation of mind wandering using tDCS was previously studied (Axelrod et al., 2015; Kajimura and Nomura, 2015). Axelrod and colleagues (2015) employed a SART paradigm to study mind wandering. They found that anodal (excitatory) stimulation over the dorsolateral prefrontal cortex increased the propensity to mind-wander relative to occipital stimulation and sham stimulation. This indicates that the frontal lobes are causally involved in mind wandering but not the occipital lobe. In another study, Kajimura and Nomura (2015) stimulated the inferior parietal lobule (IPL) and lateral prefrontal cortex (LPFC) using anodal (the anode was placed over the right IPL and the cathode over the left LPFC) or cathodal (cathode was positioned over the right IPL and the anode over the left LPFC) tDCS in two different groups, and another group underwent sham stimulation. After the stimulation a perceptual load task was administered (Lavie and Cox, 1997): participants searched for possible target letters among central non-target letters. During the perceptual load task thought probes, which required the participants to classify the contents of their thoughts, were administered. The study revealed that mind wandering propensity was significantly decreased in the anodal tDCS group compared to the cathodal tDCS group. Specifically, mind wandering propensity was reduced by anodal tDCS over the right IPL and cathodal tDCS over the left LPFC compared to cathodal/anodal tDCS of the same sites. These results are in line with findings by Axelrod and colleagues (2015), indeed, in both studies anodal stimulation over the LPFC augmented the propensity to mind-wander. Moreover, Kajimura and Nomura (2015) showed also evidence that cathodal/anodal tDCS over the left LPFC and the right IPL, respectively, diminished mind wandering. Again, results suggest a critical role of the lateral frontal lobes in mind wandering, showing that inhibitory effects of (cathodal) tDCS over the LPFC may diminish mind wandering and excitatory tDCS effects in the same site may increase propensity to mind-wander.

Here, we first localized the brain region within the mPFC more consistently associated with mind wandering conducting an activation likelihood estimation (ALE) meta-analysis on neuroimaging studies that investigated mind wandering and spontaneous cognition. We then recruited three groups of healthy individuals who performed the CRT task with thought probes (see Experiment 4) both before and after tDCS stimulation. In one group, cathodal tDCS was applied to mPFC (mPFC-tDCS), in a second group cathodal stimulation was applied to the occipital cortex (OC-tDCS) as a control region, and the third group underwent sham stimulation, in which the tDCS device was turned off after a few seconds. We found that cathodal stimulation over mPFC provoked a decreased propensity for mind wandering compared to sham and OC-tDCS groups, but only in males.

9.2 Methods

9.2.1 Meta-analysis of neuroimaging studies of mind wandering

9.2.1.1 Inclusion and exclusion criteria

To determine neuroimaging studies that investigate mind wandering, we conducted a search of the literature using PUBMED (http://www.ncbi.nlm.nih.gov/pubmed) for papers containing the words “mind wandering”; “spontaneous thought”; “stimulus-independent thought”; “task-unrelated thoughts”; or “daydreaming” from the first published neuroimaging study on spontaneous cognition (Mcguire et al., 1996). The final search was conducted on May 31, 2014. We selected only papers that reported functional neuroimaging studies (i.e., fMRI or PET). The studies had to report specific peak foci of activation in a standard reference frame (MNI or Talairach space), report group results, and involve healthy participants. Included studies had to employ some form of reports that indicated experiences of spontaneous thoughts (e.g., retrospective or online reports, or questionnaires). For papers showing more than one experiment with independent samples, each experiment was considered individually (e.g., Mcguire et al., 1996). Experiments on spontaneous cognition in which mind wandering was not explicitly measured were not considered in this meta-analysis (e.g., Christoff, Ream, & Gabrieli, 2004). Studies that reported Region Of Interests analysis were excluded as they are not compatible with the ALE meta-analysis. We excluded studies that reported contrasts calculated on two conditions that have similar processes in common. For example, studies were excluded when they reported tasks that involved internal thinking and those tasks were compared/contrasted to rest/navigation conditions (e.g, D’Argembeau et al., 2005; Spiers & Maguire, 2006a, 2006b). Table 13 shows the list of included studies.

9.2.1.2 The ALE

Analyses were conducted using GingerALE, Version 2.3 (http://brainmap.org/ale/). GingerALE is used for performing meta-analyses of human brain imaging studies with published coordinates. The ALE method is typically used to identify concordance across imagining studies of a cognitive process.

A detailed description of the ALE meta-analysis procedure can be found elsewhere (Turkeltaub et al., 2002, 2012; Eickhoff et al., 2009, 2012). Here, the procedure will be summarized. To find convergences of peak coordinates across contrasts, the reported foci for each study are modeled as the center of a Gaussian probability distribution whose width is empirically determined and automatically included (Eickhoff et al., 2009). Probability values of all foci in a particular experiment are calculated and combined for each voxel, resulting in a Modeled Activation map that represents a summary of the results of that specific experiment taking into account the spatial uncertainty associated with each reported coordinate. Next, ALE scores are calculated by taking the union of these individual Modeled Activation maps. In order to calculate each Modeled Activation map, a non-additive ALE method was chosen to restrict the number of inflated ALE values resulting from contrasts with many closely located activation foci. This method was employed to reduce the risk for within-experiment effects rather than the between-experiment concordance to be the cause of significant ALE values (Turkeltaub et al., 2012). The significance of ALE values is assessed using a random-effects significance test against the null hypothesis that localization of activity is independent between studies. To correct for multiple comparisons, we used cluster-level inference. A cluster forming threshold of P < 0.001 (uncorrected at the voxel-level) was used and the size of the resulting supra-threshold clusters was compared (with a threshold of P < 0.05) to a null distribution of cluster sizes determined by 1000 random permutations of the data (Eickhoff et al., 2012; Stawarczyk and D'Argembeau, 2015). When a foci file is opened with GingerALE, the coordinates are compared against a mask defining the outer limits of Talairach (or MNI) space. A less conservative (larger) map size was employed. Three coordinates fell outside the mask. In order to avoid omissions of information they were included into the analysis (note that similar results were obtained also excluding those coordinates). We analyzed a total of 151 foci from 10 neuroimaging studies (see Table 13).

Table 14 shows clusters of brain activation from the ALE meta-analysis. Brain areas commonly active across different neuroimaging studies during mind wandering are mainly parietal, temporal, and frontal and correspond generally to the main nodes of the DMN (Buckner et al., 2008) that was found critical for spontaneous cognition (e.g., Andrews-Hanna et al., 2010a). The larger cluster involved parieto-temporal-occipital regions, showing peak coordinates in BA 39 and BA 19, two brain regions that are often active during self-related and social-related processing (e.g, Murray, Schaer, & Debbané, 2012). A second cluster includes temporal regions, BA 36 and 37, likely related to remembering autobiographical event and simulating future experiences (e.g., Botzung, Denkova, & Manning, 2008). A third cluster, the insula/claustrum, may be associated with the ability to switch from external to internal focus of attention and vice versa (see Andrews-Hanna, Smallwood, & Spreng, 2014). Finally, the last two clusters (in terms of extension) encompassed the frontal lobe with a prevalence of activity in the left BA 10. Specifically, the larger cluster (frontal cluster 1) show a peak of activation in x = -8, y = 50, z = -8 (Talairach space). These coordinates were employed in our tDCS experiment.

Table 13. Studies included in the meta-analysis

Study	N	Foci	Mind wandering	Condition
a. Mcguire et al., 1996 – Study 1	5	5	Retrospective	Correlation between regional cerebral blood flow and stimulus independent thoughts
b. Mcguire et al., 1996 – Study 2	6	1	Retrospective	Correlation between regional cerebral blood flow and stimulus independent thoughts
c. Binder et al., 1999	30	8	Inferential	Rest - tone
d. Mason et al., 2007	19	31	Inferential and questionnaire	Practiced blocks > novel blocks; Correlation with daydreaming questionnaire
e. Christoff et al., 2009	15	17	Online	Activation before mind wandering reports
f. Wang et al., 2009	12	8	Questionnaire	Correlation between regional homogeneity and spontaneous thoughts
g. Dumontheil et al., 2010	16	18	Retrospective	Condition 1: mind wandering
h. Stawarczyk et al., 2011	22	28	Online	Mind wandering, external distraction, task related interference > on-task
i. Hasenkamp et al., 2012	14	18	Online	Awareness of mind wandering > mind wandering; Mind wandering > shift
j. Kucyi et al., 2013	51	17	Online	Mind wandering > pain

Note. N = sample size; Mind wandering = how mind wandering experiences were collected; condition = experimental condition added to the ALE meta-analysis.

Table 14. Brain area commonly activated during spontaneous cognition

Cluster	Size (mm^3)	Extreama value	Peak in Talairach			Areas	Studies contributing to the cluster
			X	Y	Z		
1. Temporo-parieto-occipital cluster	960	0.014	-42	-70	26	39/19	c, d, f, h, i, j
		0.013	-44	-74	20		
		0.013	-38	-80	18		
2. Temporal cluster	688	0.019	-28	-38	-12	36/37/20	c, f, h, j
3. Insula/claustrum	648	0.014	36	-2	10	13, insula, claustrum	d, g, i
		0.013	42	0	4		
4. Frontal cluster 1	352	0.015	-8	50	-8	10	d, h
5. Frontal cluster 2	320	0.011	0	52	8	10/32	h, j
		0.011	-2	54	2		

Note. a: Mcguire et al., 1996 – Study 1; b: Mcguire et al., 1996 – Study 2; c: Binder et al., 1999; d: Mason et al., 2007; e:(Christoff et al., 2009); f: Wang et al., 2009; g: Dumontheil et al., 2010; h: Stawarczyk et al., 2011; i: Hasenkamp et al., 2012; j: Kucyi et al., 2013.

9.2.2 tDCS experiment

9.2.2.1 Participants

Seventy-two healthy right-handed participants with no history of neurological or psychiatric disease participated in this study (for demographic information see Table 15). Participants were randomly assigned to three groups: medial prefrontal cortex (mPFC-tDCS) group, occipital cortex (OC-tDCS) group, and a sham group (types of stimulation and location of the electrodes are explained in the next paragraph). Participants were all blind to the group they belonged to. Group (mPFC-tDCS, OC-tDCS, Sham) x Gender (Male, Female) analyses of variance (ANOVA) revealed no differences across participants in terms of age ($F < 2.8$, $p > 0.06$) and years of education

($F < 0.52$, $p > 0.59$). They 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.

9.2.2.2 tDCS

Direct current (2 mA, 15 minutes) was delivered by a constant current electrical stimulator (DC STIMULATOR PLUS) connected to a pair of electrodes. The electrodes used for tDCS were covered by saline-soaked sponges (scalp electrode size: 35 cm^2; deltoid electrode size: 40 cm^2). We ramped the current up over the first 15 s of stimulation and down over the last 15 s. To guarantee safety we applied a current at a density of 0.057 mA/cm^2 (calculated on the scalp electrode) and 0.05 mA/cm^2 (calculated on the deltoid electrode). Two different montages were employed.

In 24 participants (mPFC-tDCS group; 12 males), the cathode was located on the forehead (BA 10) and the center of the electrode was placed on the left side of Fpz (10-20 system). This location was chosen based on the ALE meta-analysis. The findings of the ALE meta-analysis showed two frontal clusters, both revealed a main activation of BA10, and the larger cluster indicated a peak of activation in $x = -8$, $y = 50$, $z = -8$ (Talairach space). This peak of activation was transformed in 10-20 electroencephalography system coordinates using the Münster T2T-converter software (Deppe et al., 2003) (wwwneuro03.uni-muenster.de/ger/t2tconv/; see Figure 16A and 16B). To place the center of the electrode on the scalp, the distance of the scalp position from Cz was calculated for each participant using participants' Fpz-Cz distance, their T3-Cz distance, and using the 10-20 reference coordinates provided by Münster T2T-converter corresponding to the position $x = -8$, $y = 50$, $z = -8$ (2D coordinates: $x = -0.5$, y = 1.8). As shown in Figure 16A, in Münster T2T-converter the portion of the scalp covered by the 10-20 system is mapped to $[-2,2]^2$. Cz represents the origin of the coordinate system and each other 10-20 electrode position is mapped to an integral coordinate. Any other point in this representation can be mapped back to the scalp by interpreting its 2D coordinate relative to the locations of the surrounding 10-20 electrodes.

In other 24 individuals (OC-tDCS group; 12 males), the cathode was placed over the occipital cortex (10-20 system: Oz). In both groups cathodal stimulation was employed and in both cases the reference electrode was placed over the right deltoid muscle. This extracephalic montage maintains a low impedance and the current travels ventrally from the frontal surface to the right arm, stimulating the most ventral portion of the prefrontal cortex (Holdefer et al., 2006; Miranda et al., 2006; Fumagalli et al., 2010). Extracephalic montages might create larger total current densities in deeper brain regions. Indeed, increasing the distance between the anode and the cathode, as it occurs in an extracephalic montage, leads to stimulate regions located deeper in the brain (Miranda et al., 2006; Noetscher et al., 2014).

In a different sample of 24 participants (sham group; 12 males) the stimulator was turned off after 30 s (cathodal stimulation). Thus, participants felt the initial itching sensation associated with active tDCS, but they received no active current for the rest of the stimulation period. This method has been shown to be trustworthy in experts and non-experienced participants (Gandiga et al., 2006). In sham group the same montage of mPFC-tDCS group was employed.

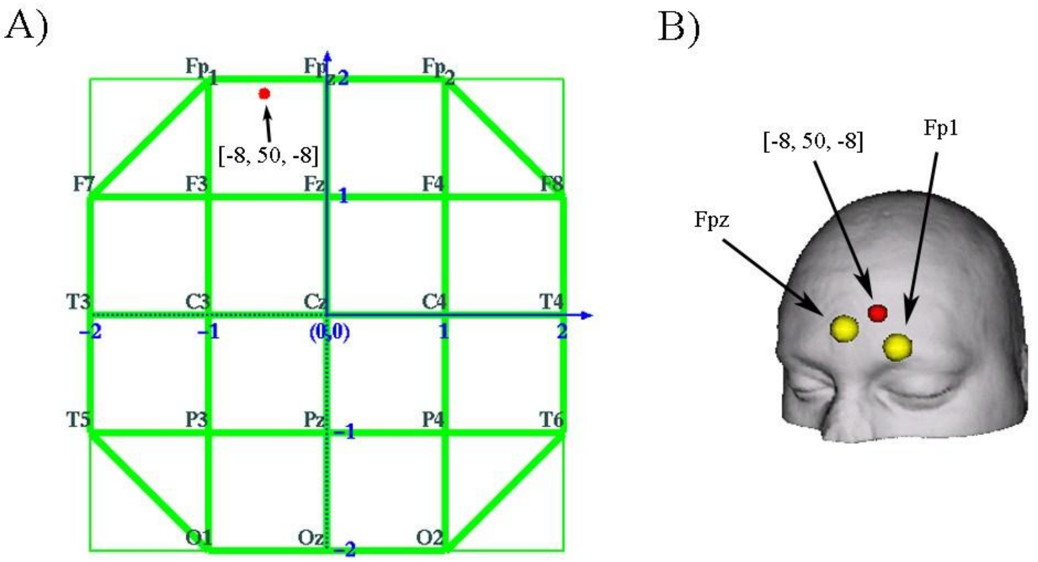

Figure 16. 2D map of the 10-20 system. The red dot represents BA 10 (x = -8, y = 50, z = -8 in Talairach space) (Panel A). 3D representation of the positions of Fpz, BA 10 (x = -8, y = 50, z = -8 in Talairach space), and Fp1(Panel B). Figure was created using Münster T2T-converter (wwwneuro03.uni-muenster.de/ger/t2tconv/; Deppe et al., 2003).

9.2.2.3 Tasks

9.2.2.3.1 Daydreaming frequency subscale

Before starting the experimental session participants completed the daydreaming frequency subscale of the Imaginal Processes Inventory (IPI, Singer and Antrobus, 1972), a questionnaire designed to examine individual differences in inner mental life. In a series of 12 daydreaming items, individuals rated the extent to which they experienced mind wandering in their daily life (e.g., “Whenever I have time on my hand I daydream”, from 1 – Never to 5 – Always). The score ranges from 12 to 60, with higher scores indicating a higher propensity toward daydreaming.

9.2.2.3.2 The 3-back task

After completing the daydreaming frequency subscale all participants were evaluated on working memory, an aspect of executive functioning that may have an impact on mind wandering (Teasdale et al., 1995; Levinson et al., 2012; Kam and Handy, 2014). Working memory was assessed with a 3-back task (based on Zimmermann & Fimm, 2002), which requires to monitor a series of numbers (from 1 to 8), and signal, using the spacebar, whether the number currently presented matches the number presented three trials back. Each number was presented for 2000 ms and interspersed with fixation crosses lasting 1500 ms. There were 100 stimuli in total and 15 possible correct responses. Correct responses, false alarms, and reaction times were recorded.

9.2.2.3.3 Choice Reaction Time (CRT) task

Participants then underwent a choice reaction time (CRT) task modified from previous studies (Smallwood et al., 2009, 2011b). The CRT task was performed by participants before and after the tDCS or sham stimulation. In the CRT task, individuals saw a stream of digits (1-8), written in a black ink and appearing in the center of the screen (non-target stimuli) or digits written in green (target stimuli). Upon presentation of a green digit, participants had to report whether that number was even or odd using the keyboard. A total of 312 non-targets and 50 targets were presented. Non-target and target stimuli were arranged in ten blocks containing approximately 5 targets and 31 non-targets each, so to have the targets roughly distributed all over the entire task. The order of the ten blocks was randomized for each participant. Presentation rate was 1 item every 1500 ms for non-targets and 1 item every 2000 ms for targets (with a 2000 ms fixation cross).

Mind wandering was assessed through the presentation of 10 thought probes, one for each block. The distance between two thought-probes varied from 20 to 50 presented stimuli in order to avoid predictability of the thought-probes occurrence. The thought-probes were presented visually on the computer screen. Firstly, participants were required to rate the locus of their current thoughts using a visual analog scale (from 0 – completely on-task to 100 – completely off-task). If participants provided an answer from 1 to 100, they were then invited to classify their thoughts in one of 6 categories: 1) Past (i.e., thoughts that involved past events; e.g. "My latest trip to Rome was the best"); 2) Future (i.e., thoughts that involved future events; e.g. "Next week I will go to the dentist"); 3) Present (i.e., thoughts about events that occur in the present moment; e.g. "I wonder what my wife is doing now"); 4) Current distractions (i.e., thoughts that involved current distractor stimuli unrelated to the task; e.g., "I'm hearing thunder") 5) Time not clear (i.e., when a thought is not easily classified into time categories, e.g. "I'm lucky to have a friend like him"); 6) Unaware (i.e., not aware about the contents of thoughts). If participants provided an answer from 1 to 5 (meaning they were aware of the contents of their thoughts), they further classified them into one of 3 'target categories': 1) Self (i.e., self-related thoughts; e.g., "I am going to bed after this"; 2) Other people (i.e., other-related thoughts; e.g., "My son is growing up so fast"); 3) None (i.e., when a thought does not involve a person; e.g., "The new car was a good deal").

Before the start of the CRT task, participants familiarized with the concept of mind wandering, off-task thought and on-task thought. We told them that individuals' thoughts may occasionally depart from current activities, and focus instead on something unrelated to the task at hand. We paid attention not to give either a positive or negative connotation of mind wandering so to avoid social desirability biases. We provided an example of mind wandering: mentally planning the next vacation while washing the dishes. We told them that thoughts deviating from the task at hand were to be considered off-task (next vacation), whereas thoughts focused on the current activity (washing dishes) were to be considered on-task. We then explained further the distinction between on-task and off-task thought in the context of our experiment. On-task thoughts were those strictly related to the computerized tasks, in which attention is completely directed toward the task, that is when individuals think about the stimuli and task procedures (e.g., “I have to answer because this number is green”), whereas off-task thoughts were those unrelated to the current activity (e.g., “After, I’ll go to the supermarket”). We have also provided examples of off-task thoughts for each category (examples that we reported before to describe the content categories).

9.2.2.3.4 Discomfort after the stimulation

Participants in all groups (mPFC-tDCS, OC-tDCS, Sham), immediately after the stimulation, were asked to rate on a 5-point Likert scale the discomfort experienced during the stimulation (from 1: “no discomfort” to 5: “extreme discomfort”).

9.3 Results

9.3.1 The daydreaming frequency subscale

Daydreaming frequency scores were generally non-normally distributed (Kolmogorov-Smirnov test, $d > 0.16$, $p < 0.05$), therefore non-parametric analysis was employed. A Kruskal-Wallis ANOVA with Group as factor (Sham-males, Sham-females, mPFC-tDCS males, mPFC-tDCS females, OC-tDCS males, OC-tDCS females) showed no significant differences across groups ($p = 0.36$). These findings indicate that groups (and genders) were matched in terms of frequency of daydreaming.

9.3.2 The 3-back task

Because working memory may support mind wandering (e.g., Levinson, Smallwood, & Davidson, 2012; Teasdale, Proctor, Lloyd, & Baddeley, 1993), we analyzed group differences in working memory capacity. The 3-back task accuracy (correct response rate – false alarms rate) and reaction times of correct answers were analyzed separately using a Group (mPFC-tDCS, OC-tDCS, sham) x Gender (Male, Female) ANOVA. No significant differences on accuracy on the 3-back task were found across groups and genders ($p > 0.36$). The same ANOVA on reaction times showed no significant main effects or interactions ($p > 0.47$). These findings show that participants, across groups and genders, have similar working memory abilities.

9.3.3 CRT Task

9.3.3.1 Accuracy and reaction times

Mean accuracy (ACC; number of correct odd/even responses) and reaction times (RT) for correct answers in the CRT task were calculated separately for each participant before and after the stimulation. We analyzed possible group and gender differences in the performance of CRT task before the stimulation. A Group (mPFC-tDCS, OC-tDCS, sham) x Gender (Male, Female) ANOVA on the accuracy for correct responses showed no significant main effects or interactions ($p > 0.09$). The same ANOVA on RT indicated no significant effects ($p > 0.32$). Thus, before the stimulation participants showed comparable abilities in accomplishing the task.

Then, we calculated, for each participant, the difference (Δ) in accuracy and RTs in the CRT task obtained before and after the stimulation. For example, the difference in accuracy was calculated as Δ_{ACC} = mean accuracy after the stimulation – mean accuracy before the stimulation. The same formulae was employed for computing the difference in RTs (Δ_{RT}). Δ-scores were analyzed using a Group x Gender ANOVA and Fisher tests as post-hoc analyses.

Table 16 shows Δ-scores of accuracy and RTs data. We observed that the performance on CRT tasks was similar across groups and genders. A Group x Gender ANOVA on Δ_{ACC} showed no significant main effects or interactions ($p > 0.37$ in all cases). The same ANOVA on Δ_{RT} revealed no significant results ($p > 0.62$ in all cases). Again, performance on CRT task before and after the stimulation was similar (see Table 16).

Table 15. Demographic information, daydreaming frequency subscale, 3-back accuracy, 3-back accuracy RTs, and discomfort rating across groups and gender

		N	Age	Education	Daydreaming subscale	3-back (accuracy)	3-back (RTs)	Discomfort
Females	mPFC-tDCS	12	23.42(0.54)	17.08(0.36)	45.58(1.79)	0.67(0.08)	817.30(52.56)	1.33(0.14)
	OC-tDCS	12	22.17(0.34)	16.92(0.26)	48.00(1.60)	0.74(0.05)	804.34(38.77)	1.58(0.19)
	Sham	12	23.42(0.67)	16.67(0.55)	45.50(2.05)	0.68(0.05)	852.14(76.26)	1.17(0.11)
Males	mPFC-tDCS	12	23.50(0.42)	16.92(0.38)	42.25(1.76)	0.74(0.06)	882.56(62.43)	1.42(0.19)
	OC-tDCS	12	22.58(0.64)	16.42(0.52)	44.00(3.74)	0.76(0.06)	865.53(81.63)	1.33(0.14)
	Sham	12	23.75(0.66)	17.00(0.32)	42.00(2.61)	0.73(0.06)	835.22(49.51)	1.17(0.11)

Note. mPFC-tDCS = participants who underwent to cathodal stimulation on medial prefrontal cortex; OC-tDCS = participants who underwent to cathodal stimulation on occipital cortex; RTs = Reaction Times. In brackets we report the standard errors of the mean.

Table 16. Δ-scores of accuracy and reaction times across groups and gender

		Δ_{ACC}	Δ_{RT}
Females	mPFC-tDCS	-0.25(0.37)	25.97(21.35)
	OC-tDCS	0.17(0.44)	30.17(33.58)
	Sham	-0.42(0.34)	34.92(20.68)
Males	mPFC-tDCS	-0.17(0.24)	14.78(19.83)
	OC-tDCS	-0.58(0.72)	58.51(30.95)
	Sham	-0.75(0.46)	47.82(31.50)

Note. Δ_{ACC} = mean number of accuracy (number of correct odd/even responses) after the stimulation - mean number of accuracy before the stimulation; Δ_{RT} = mean number of reaction times (of correct responses) after the stimulation - mean number of reaction times before the stimulation. In parenthesis we report the standard errors of the mean.

9.3.3.2 Mind wandering

Mean ratings of mind wandering collected during the CRT task were calculated separately for each participant before and after the stimulation. Initially, we explored whether group and gender differences emerged in the propensity for mind wandering before the stimulation. A Group (mPFC-tDCS, OC-tDCS, sham) x Gender (Male, Female) ANOVA on the mean number of mind wandering ratings collected before the stimulation revealed no significant main effects or interactions ($p > 0.27$), indicating a comparable initial propensity to mind-wander across groups and genders.

Next, we calculated, for each participant, the difference (Δ) in the ratings of mind wandering obtained, in the CRT task, before and after the stimulation. The difference in the mind wandering rating was calculated as Δ_{MW} = mean number of mind wandering rating after the stimulation – mean number of mind wandering rating before the stimulation. Δ-scores were analyzed using a Group x Gender ANOVA and Fisher tests as post-hoc analyses. Figure 17 represents the Δ_{MW} by participant groups and genders. As is evident, males in mPFC-tDCS group showed a reduced Δ_{MW} compared to males in sham and OC-tDCS groups. On the other hand, a comparable trend on mind wandering propensity emerged in males in sham and OC-tDCS groups. An ANOVA on Δ-scores with Group and Gender as factors showed a significant main effect of Group ($F_{(2,66)} = 3.30$, $p = 0.043$) qualified by a significant Group x Gender interaction ($F_{(2,66)} = 3.49$, $p = 0.036$). For males, Fisher tests showed a reduced Δ_{MW} in mPFC-tDCS group relative to OC-tDCS group (-9.96 vs. 9.44, $p = 0.006$), and the sham group (-9.96 vs. 12.75, $p = 0.001$). No significant difference emerged between OC-tDCS and sham groups (9.44 vs. 12.75, $p = 0.63$). No group difference emerged in females ($p > 0.25$). The results indicate that cathodal stimulation over the mPFC diminished mind wandering propensity. However, this effect was specific in males and did not emerge in females.

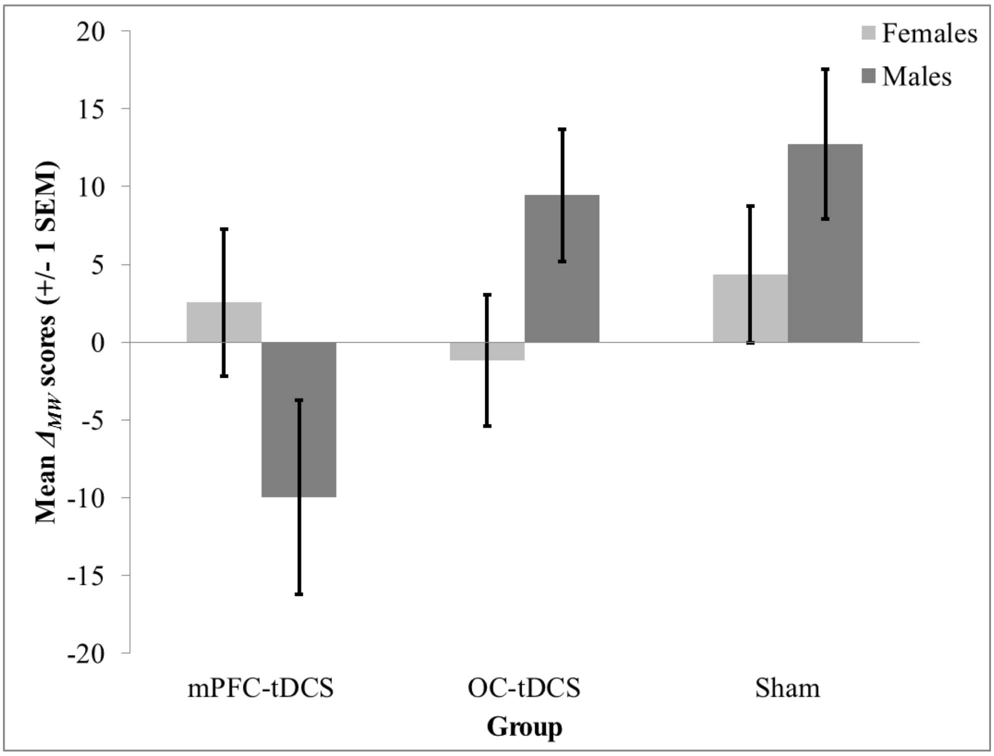

Figure 17. Mean *Δ*-scores of mind wandering by groups (mPFC-tDCS, OC-tDCS, sham) and genders. Error bars represent the standard errors of the mean (SEM).

9.3.3.3 Contents of spontaneous thoughts

We then investigated whether, in addition to the reported intensity of mind wandering, the tDCS on mPFC or occipital lobe affects the contents of mind wandering.

To perform content analyses, we counted the number of times participants described the contents of their thoughts as belonging to different categories (past, present, future, current distractions, time not clear, unaware, self-related, other-related, and unrelated to people). For past, present, future, current distractions, time not clear, and unaware categories we computed ratios dividing these numbers by the total number of mind wandering episodes claimed (i.e., receiving a rating from 1 to 100). Whereas, for self-related, other-related, and unrelated to people categories we computed ratios dividing the frequencies by the total number of mind wandering episodes claimed (mind wandering episodes that received a rating from 1 to 100) excluding the unaware thoughts (see paragraph 9.2.2.3.3). Ratios were calculated separate for CRT task before and after the stimulation and independently for each individual. Contents of mind wandering were non-normally distributed (Kolmogorov-Smirnov test, $d > 0.17$, $p < 0.05$), therefore analyses were performed using Kruskal-Wallis ANOVAs by Ranks and Mann-Whitney as post-hoc tests.

Firstly, non-parametric ANOVAs run on each content category ratios collected during CRT task before the stimulation revealed no statistically significant group or gender differences ($H < 10.81$, $p > 0.05$).

Next, Δ-scores were calculated as content ratio after the stimulation – content ratio before the stimulation, for each category ($\Delta_{CONTENT}$) and each participant. We run separate analysis in females and males on the $\Delta_{CONTENT}$. In females, no significant difference across groups of stimulations was found (Kruskal-Wallis ANOVAs: $H < 0.34$, $p > 0.18$).

In males, non-parametric ANOVAs on $\Delta_{CONTENT}$ revealed a significant main effect of group for other-related contents ($H = 7.40$, $p = 0.02$), showing a lower Δ_{OTHER} in sham group than Δ_{OTHER} in mPFC-tDCS group (-0.246 vs. -0.069, $z = -2.02$, $p = 0.04$) and a lower Δ_{OTHER} in sham group relative to Δ_{OTHER} in OC-tDCS group (-0.246 vs. 0.016, $z = -2.37$, $p = 0.02$), but no differences between mPFC-tDCS and OC-tDCS groups ($p = 0.24$). These findings indicated that participants in the sham group produced more rarely other-related thoughts after the stimulation (relative to other-related thoughts before the stimulation), whereas the same decrease in other related thoughts was not observed after mPFC-tDCS and OC-tDCS stimulation. No other significant main effects of group emerged ($p > 0.09$). Observing the means of contents ratios before and after the stimulation separately for each group in males, we noted that, only in the sham group after the stimulation there was an enhanced self-referential effect and a diminished other-referential effect relative to before the sham stimulation. This observation was supported by statistical analysis: only participants belonging to sham group showed a significant higher self-related thoughts ratio after the stimulation compared to before (before: 0.28 vs. after: 0.39, Wilcoxon test: $z = 1.89$, $p = 0.05$). The opposite occurred for other-related contents (before: 0.45 vs. after: 0.20, $z = 2.76$, $p = 0.006$). This effect was not present in the other two groups ($p > 0.17$). Thus, in the sham group, the decrease in other related thoughts with time came along with an increase in self-related thoughts. When the mPFC or the occipital lobe are inhibited by the stimulation this effect was abolished. Hence, these results may suggest an involvement of mPFC and occipital lobe in sustaining self-related (as opposed to other-related) thoughts.

Table 17. Contents (*Δ-scores ratios*) of mind wandering episodes

		Δ_{PAST}	$\Delta_{PRESENT}$	Δ_{FUTURE}	$\Delta_{DISTRACTIONS}$	$\Delta_{T\_NOT\text{-}CLEAR}$	$\Delta_{UNAWARE}$	Δ_{SELF}	Δ_{OTHER}	Δ_{NONE}
F	mPFC-tDCS	0.024 (0.044)	0.024 (0.047)	-0.030 (0.050)	-0.083 (0.011)	0.057 (0.040)	0.008 (0.019)	0.018 (0.083)	0.037 (0.082)	-0.055 (0.036)
	OC-tDCS	-0.058 (0.034)	-0.050 (0.069)	0.108 (0.051)	-0.050 (0.048)	0.008 (0.040)	0.042 (0.040)	0.041 (0.091)	0.003 (0.041)	-0.044 (0.068)
	Sham	0.004 (0.057)	-0.046 (0.063)	0.045 (0.052)	-0.042 (0.043)	-0.004 (0.045)	0.043 (0.020)	-0.005 (0.053)	-0.042 (0.069)	0.046 (0.058)
M	mPFC-tDCS	-0.034 (0.036)	-0.075 (0.071)	-0.034 (0.042)	-0.033 (0.032)	0.124 (0.046)	0.054 (0.060)	-0.009 (0.078)	-0.069 (0.044)	0.079 (0.052)
	OC-tDCS	-0.026 (0.057)	-0.190 (0.079)	0.084 (0.079)	0.015 (0.085)	0.133 (0.082)	-0.017 (0.017)	-0.094 (0.075)	0.016 (0.085)	0.078 (0.068)
	Sham	0.025 (0.058)	-0.053 (0.038)	0.025 (0.061)	-0.041 (0.035)	0.012 (0.044)	0.032 (0.023)	0.110 (0.057)	-0.246 (0.064)	0.136 (0.026)

Note. F = females; M = males; mPFC-tDCS = cathodal stimulation on medial prefrontal cortex; OC-tDCS = cathodal stimulation on occipital cortex; T_NOT-CLEAR = time not clear. In parenthesis we report the standard errors of the mean.

9.3.4 Discomfort after the stimulation

Finally, we analyzed possible differences on discomfort experienced during the stimulation across groups and genders. Discomfort ratings were non-normally distributed (Kolmogorov-Smirnov test, $d > 0.43$, $p < 0.01$), therefore Kruskal-Wallis ANOVAs by Ranks were employed.

As it is possible to observe from Table 15, discomfort ratings were substantially low and similar across groups (Sham-males, Sham-females, mPFC-tDCS males, mPFC-tDCS females, OC-tDCS males, OC-tDCS females): a Kruskal-Wallis ANOVA showed no significant main effects or interactions on discomfort rating ($H = 4.76$, $p = 0.45$). Also, Spearman correlation analyses revealed no significant correlations between Δ_{MW} and discomfort ratings in each group (all p values > 0.28), suggesting that there is no association between discomfort and mind wandering.

9.4 Discussion

In the current experiment we aimed to investigate the causal role of mPFC in supporting mind wandering. Using an ALE meta-analysis we investigated which brain regions are consistently active during mind wandering. Then, we employed peak coordinates resulted from that meta-analysis to stimulate the mPFC (BA 10), in order to modulate the propensity to mind-wander employing tDCS. Previous experimental findings demonstrated that several regions belonging to the DMN are active during mind wandering (Buckner et al., 2008; Andrews-Hanna et al., 2010a), such as fronto-temporal-parietal regions, including occipital areas and insula (Fox et al., 2015). The brain regions resulted from the current ALE meta-analysis reveal consistent activation in BA 39, 19, 10, 32, 36, and 13 (see also Fox et al., 2015). Brain areas, that we found active during mind wandering are overall linked to the capabilities to remember, imagine the future, navigate, simulate complex experiences, or mentalizing. These mental activities may occur also spontaneously and, thus, may represent typical contents of mind wandering experiences (Spreng et al., 2009; Andrews-Hanna et al., 2010b, 2014). Several studies showed that the mPFC contributes to support mind wandering and deliberate MTT (e.g, Andrews-Hanna et al., 2014). Moreover, in previous experiments we found that the ventral part of the mPFC, including BAs 10, is critical for supporting the simulation of any kind of complex experience (see Experiments 1, 2, and 3) also for mind wandering (see Experiment 4). The current ALE meta-analysis revealed two clusters of activation of frontal lobes. Those clusters include mainly BA 10 and also BA 32, in addition other regions in the parieto-occipital cortex (BAs 39, 19), temporal lobes (BAs 36, 37), and insula/claustrum. Therefore, BA 10 may be an adequate target area to stimulate in order to modulate mind wandering propensity and, thus, coordinates of BA 10 have been employed in a tDCS experiment to reach this goal.

Findings show that cathodal tDCS over the mPFC leads to a decrement of mind wandering intensity compared to sham and occipital tDCS in males. We also confirmed results from a previous study (Axelrod et al., 2015) that the effect of tDCS on occipital cortex does not disrupt mind wandering. However, the current study differs from the previous investigation on mind wandering using tDCS (Axelrod et al., 2015; Kajimura and Nomura, 2015) because we exclusively found modulation of mind wandering propensity in males.

These results are unlikely to be due to differences between groups and genders in working memory capacity, that is an ability critical for supporting mind wandering (Teasdale et al., 1993; Kam and Handy, 2014), because all groups were matched by working memory performance assessed at the beginning of the session. Participants were also matched by performance on CRT task before the stimulation. This result excludes the possibility that CRT task was too difficult for some participants leading to a greater engagement of resources in the task, so that those resources were not available anymore for maintaining mind wandering. Furthermore, no significant differences emerged across groups of stimulation and genders on discomfort ratings that could have affected contents and propensity to mind-wander.

Although no significant differences emerged between males and females on daydreaming frequencies, we noticed that females tended to have a higher score on daydreaming frequency scale than males (see Table 15), suggesting a higher tendency in females to mind-wander in daily life, or to notice mind wandering. Gender differences on the phenomenology of mind wandering emerged in previous works. Females reported more vivid mental imagery in mind wandering than males (Christian et al., 2013), and they tend to ruminate more often than males (Nolen-Hoeksema and Jackson, 2011; Miyamoto and Kikuchi, 2012). Sex differences emerged also in the contents of spontaneous cognition, indeed, females tend to report more often social daydreaming than males (Mar et al., 2012). Moreover, sex roles predict daydreaming. For instance, masculine, compared to feminine and undifferentiated groups, showed the leastlevel of mind wandering (e.g., Golding & Singer, 1983). If females have a general higher tendency to daydream in daily life, this could have caused an increased difficulty in modulating mind wandering using tDCS. Alternatively, females might be more accustomed to daydreaming in daily life, and therefore more able to become aware of mind wandering and exert control on its effects during performance, being less susceptible to external (tDCS) stimulation.

Interestingly, other tDCS studies showed differential effects on task performance according to the gender (Boggio et al., 2008; Fumagalli et al., 2010; Lapenta et al., 2012; Conson et al., 2015). In those studies tDCS stimulation was applied over different brain regions (left temporal, dLPFC, mPFC, and superior temporal cortex) and while performing different tasks (facial expression recognition, utilitarian decisions, and speech perception). Results demonstrated that stimulation affected performance differentially in females and males, also provoking opposite results (e.g., Boggio et al., 2008). Therefore, a possible explanation to the gender difference in modulation of mind wandering could be a different brain connectivity in male and female participants. In a resting state fMRI study, greater regional homogeneity was shown in females compared to males in the right middle cingulate gyrus, right fusiform gyrus, left inferior parietal lobule, left precentral gyrus, left supramarginal gyrus, and left postcentral gyrus (Xu et al., 2015). In another study, gender differences were also found in gray matter density. Females showed higher grey matter density than males in parahippocampal gyrus, middle frontal gyrus/orbital, superior frontal gyrus, superior frontal gyrus, cerebellum, and cuneus (Wang et al., 2012). Another study showed better communication between hemispheres in females (Ingalhalikar et al., 2014). A higher proportion of myelinated fibers within hemispheres were found in males. In this study results suggest that male brains have a superior communication within the hemispheres, whereas female brains perform better in interhemispheric communication. Interhemispheric connectivity dominance in females was present mainly in the frontal lobe during adolescence but was more distributed during adulthood (Ingalhalikar et al., 2014). Males and females may also differ in terms of brain activity during autobiographical memory retrieval, and autobiographical memories are a typical content of mind wandering experiences (see 3.1). Females showed increased hemodynamic activity compared to males in the dLPFC, dorsal anterior insula, and precuneus while recalling specific autobiographical memories (Young et al., 2013). Together these studies show that males and females have differences in brain structural and functional connectivity. Taking into account the several studies that found gender differences on the effects of tDCS, we hypothesize that stimulation may have affected differently males and females because females could have shown a better compensation/ re-organization of brain connectivity during and after the stimulation. However, further studies are necessary to better understand gender differences in brain activity and if and how this may influence spontaneous cognition.

Results on content of mind wandering experiences showed differences on self-related and other-related thought frequencies between and within groups of stimulation in males. An increased self-related frequency and a decreased other-related frequencies after the stimulation emerged only in the sham group, indicating that, in normal circumstances, mind wandering tend to focus relatively more on the self than others over time. This effect was abolished by tDCS, which affected self vs. other-related processing when applied to both mPFC and the occipital cortex. There are several studies supporting the role of the mPFC in self-referential processing (see also chapter 4). For instance, it has been shown that simulating personal future events and reflecting on one’s personality traits show activation in the mPFC (D’Argembeau et al., 2010b), moreover, the mPFC is more active when thinking about personal past and future compared to simulating the non-personal past and future (Abraham et al., 2008). In an ALE meta-analysis, brain activation during self-related processing compared to other-referential processes were observed mainly in the mPFC (Murray et al., 2012). Therefore, it is not surprising that an inhibition of the mPFC may provoke a reduced frequency of self-referential thoughts. Interestingly, our results showed also that occipital cortex may contribute to self/other related processing. In a fMRI study by Herold and colleagues (2015), participants were shown self-referential and non-self-referential (but conveying social information) pictures. Participants had to answer questions about self-referentiality of the stimulus (“Does this picture personally relate to you?”) and episodic memory retrieval (“Is this picture familiar to you?”). Brain activations show different effects on self-referential processing compared to social processing, in various regions of the mPFC and parietal lobe but additional activation was found in occipital cortex (Herold et al., 2015). Moreover, occipital areas are also involved in supporting egocentric reference frames. In an fMRI study (Saj et al., 2014), participants evaluated the alignment of a bar relative to the middle of their body (egocentric) or another stimulus (allocentric) during fMRI. Results demonstrated that the occipital areas are active preferentially during taking egocentric perspectives. A possibility is that the occipital cortex is important for self-related (egocentric) processing as is mPFC. Another possibility is that self-related processing is more complex than other-related processing, and therefore interference with any brain region would hinder performance. However, other studies are necessary to specifically test this hypothesis.

To sum up, we have found that applying cathodal tDCS over the mPFC affects the degree to which individuals engage in mind wandering experiences but this does not occur when occipital cortex was stimulated. However, this effect was specific in males. These findings reinforce our interpretation of medial prefrontal regions as crucial to support mind wandering. Moreover, they suggest the possibility that the content - not only the frequency - of mind wandering can be modulated by tDCS, paving the way to future studies on the neural bases mediating different aspects of the phenomenology of self-reflection.

10 General discussion

The experiments we conducted allowed us to answer several questions we formulated earlier in the introduction (see chapter 1). Firstly, we demonstrated that the vmPFC supports equally the capability to remember the past and to imagine the future but also the ability to imagine episodes belonging to other individuals. Secondly, we discovered that vmPFC is critical for the construction of complex coherent mental scenarios as well as those that are not staged in a particular time. However, a lesion to vmPFC affects more markedly the ability to imagine personal future events than the ability to imagine fictitious experiences. Thirdly, we revealed that the results we found are not explained by non-episodic processes, such as narrative or working memory abilities. Therefore, vmPFC plays a specific role in constructing experiences that allow individuals to imagine scenarios alternative to the present and its role is not mediated by other non-episodic abilities. Finally, we highlighted for the first time, in two experiments using a lesion approach, the involvement of the vmPFC in mind wandering.

Considering the brain like a network of areas that work in concert to allow individuals to escape from the here and now, in the present thesis I asked a main question: what happens to the experience of MTT when a node of this network, in our case the vmPFC, does not work properly? A lesion to the vmPFC provokes a reduced ability to simulate complex experiences alternative to the present, when individuals deliberately remember episodes and imagine novel experiences and also when their attention shifts away from the main task toward off-task thoughts in a spontaneous way. Our findings reflect the fractionation of the DMN that Andrews-Hannah and colleagues (2010b) found in a previous study (see 4). Considering their results, vmPFC is a node of DMN part of the MTL subsystem that has been hypothesized to support self-related future decision making. Within the MTL subsystem vmPFC has connection with other brain areas, such as hippocampal formation. Moreover, vmPFC is also connected with the main core of the DMN, so with anterior medial prefrontal cortex and posterior cingulate cortex, but also its activity correlates with the dLPFC system that is hypothesized to be involved in mentalizing. Therefore, in line with the fractionation of the DMN, a lesion in vmPFC is likely to cause a disconnection with the other subsystems and the consequence will be a reduced capability to simulate any kind of complex experience, as we found in our experiments. Thus, it is likely that vmPFC works in concert with other brain regions, such as the MTLs, for allowing the individuals to escape from the here and now.

vmPFC might be important for integrating different episodic, affective, and perceptual details necessary for retrieving and imagining complex experiences (see also Benoit, Szpunar, & Schacter, 2014; Nieuwenhuis & Takashima, 2011; Zeithamova, Dominick, & Preston, 2012). In previous literature Nieuwenhuis and Takashima (2011) suggested that the vmPFC likely integrates information which is represented in separate areas of the limbic system. This integration of information may become more important over time, thanks to the involvement of the vmPFC in memory consolidation. Also Benoit and Schacter (2014) hypothesized that vmPFC may be necessary for the integration of knowledge that is present in different cortical regions during the simulation of complex experience, such as imagining the interaction with other individuals. It is possible that vmPFC is necessary for integrating different kinds of information in a whole coherent picture of the episode/scenario. The role of vmPFC as an "integrator" may explain the result that vmPFC patients were not able like controls to construct fictitious experiences, showing also a diminished capacity to integrate details in a spatial coherent manner, indeed, vmPFC patients demonstrated to possess a lower spatial coherence index than control groups (see Experiment 2).

However, our findings indicate that the vmPFC patients' deficits in EFT was more pronounced compared to their deficit in constructing fictitious scenarios, suggesting that vmPFC is particularly engaged in EFT. A possible reason why vmPFC patients had deeper impairment in EFT is that sub-regions that belong to the vmPFC have different roles in supporting complex experiences and EFT. In our studies we found evidence to support this hypothesis. In Experiment 1, despite the fact that a small group of patients were tested, findings showed that EFT correlated with lesion volume in two areas part of the vmPFC: BA 11 and BA 32. Moreover, correlation analyses in Experiment 2 suggested that general deficits in scene construction and specific deficits in EFT may have different roots within vmPFC. Lesion volume in BA 11 correlated negatively with a measure of the quality of imagining future and fictitious scenarios, suggesting that the most ventral part of vmPFC may mediate constructive processes needed to simulate any novel event. Differently, lesions in BA 10 and BA 32 had a specific impact on the EI for future scenarios. As we mentioned before, lesion volume in BA 10 correlated positively and lesion volume in BA 32 correlated negatively with the EI. A reduced input from BA 10 may have protected vmPFC patients from memory-interference during EFT. On the other hand, the BA 32 may help control interference from similar episodic memories, allowing construction of future events that reflect relevant and updated self-knowledge. According to these results and observations, we speculate that BA 11 may support the construction of any kind of complex experiences, whereas, BA 10 and 32 may be sensitive to experimental conditions that load maximally on MTT processes, such as during future thinking, when individuals have to filter out irrelevant information in order to imagine plausible novel future experiences.

This reduced ability to construct complex experiences may also be linked to the impoverished capability to mind-wander that emerged in vmPFC patients. Mind wandering might be considered as a type of spontaneous process of MTT and scene construction, hence, the inability to create complex mental experiences may have affected also the quality and the genesis of spontaneous cognition. If vmPFC patients have lost the neural foundation needed to construct events alternative to external reality, there would be no internal event capable to generate the internal train of thoughts typical of mind wandering experiences. vmPFC damage may decrease mind wandering by reducing the content of mind wandering experiences. Thus, reduced mind wandering, MTT, event construction are likely to be different expressions of the same underlying deficit in projecting one's self toward alternative realities. It would be interesting, in the future, to further investigate the differential roles of the sub-regions of vmPFC in MTT, scene construction, and mind wandering in larger samples of patients with circumscribed lesions or employing neuroimaging techniques.

Together our findings highlight the dynamic nature of memory. Individuals can, consciously or not, deliberately or not, retrieve episodes, model and manipulate them, choose some pieces, mix them together and transform them into a novel temporal or fictitious mental experience. This capability permits to navigate mentally into other places and times. We could say that probably memory is one of the most creative and malleable abilities that human beings possess and it affects pervasively individuals' lives; especially concerning modern day life. How can a person who lives entirely in the present, be able to organize events, plan actions, solve problems, anticipate possible dangers, make effective decisions and at the same time be competitive and successful at school, at work, and in the society? Well, this looks like a rhetoric question. Recent findings have shown that even during mere eye contact between two individuals the DMN is active, suggesting that DMN is pervasively engaged while interacting with other individuals, even if the interaction concerns non-verbal communication (Lee, 2015). Indeed, an intact ability to imagine different scenarios and surf across them is likely to be critical for allowing individuals to adaptively interact with each other. Let's just consider a complete opposite perspective for a moment. A number of studies investigated the importance of being in the present moment, for example the studies on mindfulness that is a practice used in different domains that promotes awareness moment by moment. It derives from a Buddhist concept that through living in the present moment, the nature of all phenomena and people is experienced. There is a large number of studies that show the advantages of mindfulness, for example, stress reduction, emotion regulation, pain reduction, etc. (Davis and Hayes, 2011; Reiner et al., 2013). Hence, there are many positive effects of not being able to escape from the here and now. Although we do not deny that there are advantages in being in the present moment, we can certainly observe that the normal balance between being in present and escaping from the here and now is disrupted in patients with vmPFC lesions.

The lesion approach, together with neuroimaging studies, offers an important and rare opportunity to investigate and understand how brain regions work and how brain networks contribute to cognition. Specifically, the lesion approach allows to study the brain and cognitive functioning when a brain area does not give a continued and intact contribution to brain functioning because of damage. In the domain of the MTT, a few studies investigated the role of frontal lobe in remembering the past and imagining the future (see 2.3). Therefore, our results revealing the importance of vmPFC in constructing and simulating experiences offer new insights into the functioning of high order cognition and may be useful to reach future new advances in the understanding how human beings create mental complex experience, and, possibly, support social interaction. Indeed, it would be interesting to study the social function of DMN investigating the brain activity of individuals, simultaneously, while communicating with each other. This experimental procedure could be implemented also in patients with brain damage (see Gordon et al., 2014; Stolk et al., 2015) to test how a lesion in the DMN may affect social communication. Another possible future project could involve the creation of specific training to help individuals having a reduced capability of remembering the past and imagining the future to improve MTT. In previous studies on patients with relapsing-remitting multiple sclerosis, who have deficits in MTT, it has been shown that a training in mental visual imagery can improve their MTT abilities (Ernst et al., 2015). Therefore, a training based on the task we utilized in our experiments, could be validated and employed to improve the capability of constructing complex scenarios in patients with vmPFC damage. Finally, in order to strengthen the validity of our findings it would be interesting to study MTT and mind wandering on patients with lesions to vmPFC using neurophysiological measures, such as electroencephalography, eye movement, and skin conductance, in real time, that can provide reliable and non-introspective measures of cognition. This would give the possibility of better understanding the neural correlates of deliberate and spontaneous cognition using a more multifaceted neuroscientific approach.

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