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Self-Related Processing and Future Thinking: Distinct Contributions of Ventromedial Prefrontal Cortex and the Medial Temporal Lobes

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Abstract

Episodic future thinking depends on a core network of regions that involves, in addition to the medial temporal lobes (MTL), the ventromedial prefrontal cortex (vmPFC). Neuroimaging studies suggest that vmPFC is particularly involved when future thinking requires consideration of self-relevant information, but lesion evidence for a special role of vmPFC in constructing self-relevant scenarios is limited. To clarify the involvement of vmPFC in future thinking, eight patients with vmPFC lesions were asked to imagine future events pertaining to the self or to another person, and their performance was contrasted with that of eight patients with MTL lesions. Patients with vmPFC lesions were no more detailed in their description of future events pertaining to the self than of events pertaining to another person. In contrast, like controls, patients with MTL lesions showed a self-benefit, despite impoverished performance overall. These findings accord with evidence from neuroimaging studies and elucidate the distinct contributions of vmPFC and MTL to future thinking.

Keywords

future thinking; self; psychological distance; amnesia; medial temporal lobe; ventromedial prefrontal cortex

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1. Introduction

Over the last decade, a substantial body of work has examined the cognitive and neural mechanisms underlying episodic prospection, the ability to imagine future events or generate hypothetical scenarios. This interest arose from neuroimaging studies demonstrating that the hippocampus is similarly engaged during episodic memory and episodic prospection (Benoit & Schacter, 2015; Buckner & Carroll, 2007; Mullaly & Maguire, 2014; Schacter, Addis, & Buckner, 2007) as well as from lesion studies revealing that patients with medial temporal lobe (MTL) lesions who cannot remember past events are also unable to vividly imagine hypothetical and future scenarios (Andelman, Hoofien, Goldberg, Aizenstein, & Neufeld, 2010; Hassabis, Kumaran, Vann, & Maguire, 2007; Kurczek et al., 2015; Race, Keane, & Verfaellie, 2011; but see Squire et al., 2010). This work has highlighted the role of the hippocampus in retrieving and recombining details in the service of the construction of novel mental events (Addis & Schacter, 2012; Schacter & Addis, 2007) and in constructing a scene that functions as the spatial scaffold in which an event unfolds (Hassabis, Kumaran, & Maguire, 2007; Maguire & Mullally, 2013).

This strong focus on the MTL notwithstanding, it also became apparent that episodic prospection, like episodic memory, depends on a core network of regions that includes, in addition to the MTL, the ventromedial prefrontal cortex (vmPFC), posterior midline regions, posterior parietal, and lateral temporal regions (Benoit & Schacter, 2015; Hassabis & Maguire, 2007; Schacter et al., 2007; Stawarczyk & D'Argembeau, 2015). The distinct contribution of these other regions of the core network, however, has received less attention. In the present study, we focus on the role of vmPFC in episodic prospection.

Neuroimaging studies have revealed that vmPFC is particularly engaged when imagining events requires consideration of information relevant to the self. That is, vmPFC shows higher activity when one is imagining a scenario pertaining to the self than to another person (De Brigard, Spreng, Mitchell, & Schacter, 2015; Szpunar, Watson, & McDermott, 2007) and when one is imagining events related to personal goals compared to events unrelated to personal goals (D'Argembeau et al., 2010). Such findings are consistent with a well-established role for vmPFC in self-referential processing (D'Argembeau & Salmon, 2012; Denny, Kober, Wager, & Ochsner, 2012; Qin & Northoff, 2011; Van der Meer, Costafreda, Aleman, & David, 2010).

In the domain of memory, evidence suggests that vmPFC is critical for the instantiation and active maintenance of cognitive schema (Ghosh & Gilboa, 2014; Gilboa & Marlatte, 2017) and the integration of novel information into these existing knowledge structures (Gilboa & Marlatte, 2017; Spalding, Jones, Duff, Tranel, & Warren, 2015; Van Kesteren, Rijpkema, Ruiter, & Fernandez, 2010). In the context of episodic simulation, vmPFC-mediated activation of schemas may afford access to related information that can be used in service of simulating a possible future scenario (Benoit, Szpunar, & Schacter, 2014). This view provides a way to understand the role of vmPFC in self-relevant simulations: the self constitutes a compelling higher order schema that organizes the defining features of one's identity that are active in the mind at any particular moment (cf. the working self, Conway, 2005). As such, one way in which vmPFC may contribute to episodic prospection is through

instantiation of a self-schema that guides access to relevant details and promotes integration of retrieved elements into a coherent scenario.

Yet, evidence from lesion studies has provided mixed evidence regarding the role of vmPFC in episodic prospection. Using the presence of personal pronouns in fictitious narratives about oneself as a measure of self-referential processing, Kurczek and colleagues (2015) found that patients with vmPFC lesions used a smaller proportion of self-referential pronouns than controls and patients with MTL lesions. Whereas this result is consistent with the view expressed above, another aspect of their findings calls into question the necessity of vmPFC for the construction of detailed novel events. Namely, they found that the narratives generated by vmPFC patients, in contrast to those generated by MTL patients, were as detailed as those of controls.

In contrast, Bertossi and colleagues (Bertossi, Aleo, Braghittoni, & Ciaramelli, 2016) found that a group of patients with vmPFC lesions were impaired in the construction of both fictitious and future scenarios. Interestingly, their patients had a more marked difficulty in imagining future events compared to atemporal scenes. The authors postulated that this might be due to greater reliance on self-related knowledge when imagining a plausible future event in comparison to constructing a scene. However, a follow-up study that manipulated psychological distance by comparing imagined events happening to oneself, to a close other, and to a distant other offered no support for this view: patients were equivalently impaired across the three conditions (Bertossi, Tesini, Cappelli, & Ciaramelli, 2016). Moreover, in contrast to the finding of Kurczek et al. (2015), the tendency to use self-referential pronouns in self-related narratives was intact.

One notable aspect of Bertossi, Tesini, et al.'s (2016) study is that psychological distance did not impact the performance of control subjects. Namely, the richness of imagined events, as measured by the number of event-specific details, was no greater for scenarios about oneself than about another person (whether close or distant). This finding is surprising given that greater psychological distance is associated with more abstract and general event representations (Liberman & Trope, 2008) and self-relevance has been shown to facilitate access to event details (D'Argembeau & Mathy, 2011; De Vito, Gamboz, & Brandimonte, 2012). The findings of Bertossi, Tesini, et al. (2016) leave open the question as to whether vmPFC patients would fail to show an effect of psychological distance under conditions in which such an effect is present in normal individuals.

The current study sought to further explore the hypothesis that the contribution of vmPFC to episodic prospection is linked to demands on self-related knowledge. To this end, we implemented a self/other manipulation that was successful in affecting the amount of event-specific detail present in simulations generated by control subjects. To assess whether any observed impairment could be linked specifically to vmPFC, we also tested a group of patients with MTL lesions. We predicted that patients with vmPFC lesions would fail to show the benefit associated with imagining a future scenario related to the self. By contrast, we expected that patients with MTL lesions would show a self-benefit, given their ability to use schema information in the service of memory (Kan, Alexander, & Verfaellie, 2009; Race, Palombo, Cadden, Burke, & Verfaellie, 2015), presumably by virtue of the integrity of

vmPFC. For the sake of comparability with previous work (Bertossi, Tesini, et al., 2016; Kurczek et al., 2015), we also examined the presence of self-referential pronouns in narratives about the self.

2. Methods

We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. Participants

The study sample consisted of eight patients with vmPFC lesions (5 women), eight patients with MTL lesions (2 women), and 32 control participants (14 women). Sample size was determined based on prior studies of future thinking in patients with vmPFC (Bertossi, Tesini, et al., 2016; Kurczek et al., 2015) or MTL lesions (Race et al., 2011). For all vmPFC patients, etiology of injury was aneurysm of the anterior communicating artery (ACoA). For MTL patients, etiology was hypoxic-ischemic injury secondary to cardiac or respiratory arrest (n=5), encephalitis (n=1), stroke (n=1), and status epilepticus followed by left temporal lobectomy (n=1). All patients were in the chronic phase of illness, with time post injury ranging from 1.8 to 25.4 years for vmPFC patients and from 1.1 to 26.4 years for MTL patients.

Demographic and neuropsychological characteristics for each patient group are provided in Table 1. For vmPFC patients, overall intellectual function was generally preserved, as indicated by verbal IQ (mean=103.1) and Working Memory Index scores (mean=99.6), as assessed by the WAIS-III, in the average range. Patients also performed in the normal range on several executive function tests, including verbal fluency (mean z=−.38) and letter-number sequencing (mean z=0). Memory performance was highly variable, as is often the case among patients with vmPFC damage secondary to ACoA aneurysm (e.g., Gilboa, Alain, et al., 2009; Ghosh & Gilboa, 2014), with poor memory thought to be due to encroachment of lesions on the basal forebrain or interruption of white matter pathways between the hippocampus and basal forebrain. For this reason, follow-up analyses were performed examining separately the performance of the three patients with “good” memory functioning (P02, P03, P04) and the remaining patients with “poor” memory functioning. The former group performed within 1 SD of the control mean on all three memory indices of the WMS-III and had a mean General Memory index of 104.3. The latter group performed more than 1.5 SD below the control mean on at least one of the three memory indices and had a mean General Memory index of 65.8. Two patients in the poor memory subgroup showed evidence of spontaneous confabulation.

Lesions for all vmPFC patients, based on most recent CT or MRI, were manually drawn onto the standard Montreal Neurological Institute brain using MRIcro software (Rorden & Brett, 2000). Lesions in the vmPFC patients involved Brodmann’s areas 4, 5, 6, 8, 9, 10, 11, 23, 24, 25, 32, 38, 46, and 47, but additionally involved basal forebrain in several patients. Overall lesion size was not significantly different in patients with good memory (mean= 22.75 cc) vs poor memory (mean=29.53cc; t<1). Figure 1 shows the extent of lesion in each

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vmPFC patient as well as lesion overlap across patients. The maximal overlap of lesions was in BA 32 (mean=6.05 cc, SD= 4.61 cc), BA 10 (mean=7.28 cc; SD=6.79 cc), and BA 11 (mean=10.46 cc, SD=9.54 cc). The average amount of lesion in vmPFC, calculated by superimposing individual scans on a template of vmPFC based on landmarks identified by Mackey and Petrides (2014), was 17.8 %. Lesions were bilateral in 5 patients, and limited to the right hemisphere in the remaining 3 patients. One patient had an additional lesion in left ventrolateral prefrontal cortex, and another patient had an additional lesion extending from the right putamen dorsally into premotor/motor areas. Excluding these patients from the analysis did not alter the pattern of results.

For each of the MTL patients, the neuropsychological profile indicated severe episodic memory impairment (mean General Memory Index=62.5) in the context of otherwise preserved cognition (mean VIQ=103.9; mean Working Memory Index=99.5). Lesions for six of the MTL patients are presented in Figure 2, either on MRI or CT images. The remaining two patients (P04, P05) who had suffered cardiac arrest could not be scanned due to medical contraindications. MTL pathology for these patients was inferred based on etiology and neuropsychological profile. For the patient who suffered encephalitis (P07), clinical MRI was acquired only in the acute phase of illness, with no visible lesions observed on T1-weighted images. However, T2-flair images demonstrated bilateral hyperintensities in the hippocampus and MTL cortices as well as the anterior insula. Volumetric data were available for four of the eight MTL patients. Three patients (P03, P06, P08) had lesions restricted to the hippocampus, with volume reductions ranging between 1.92 and 3.69 cc (22 and 46%), whereas the fourth patient (P02) had extensive volume loss in the hippocampus (4.97 cc; 63%) as well as in the left anterior parahippocampal gyrus (2.90 cc; 60%).

Overall lesion volume was greater in vmPFC patients (mean=26.99 cc) than in MTL patients for whom volumetric data were available (mean=4.13 cc). This is not surprising given the relative size difference in these two regions. However, more importantly, the percentage of MTL lesioned in MTL patients (mean=9.00%) was not significantly different from the percentage of vmPFC lesioned in vmPFC patients (mean=17.8%; $t<1$). The percentage of hippocampus lesioned in the MTL patients (mean = 44.8%) was greater than the percentage of vmPFC lesioned in vmPFC patients ($p = .038$).

Sixteen healthy control participants, with no history of neurological or major psychiatric illness, were matched to the vmPFC patients in terms of gender (10 women), age (mean=51.7), education (mean=13.9), and verbal IQ (mean=104.7). The remaining 16 healthy control participants were matched to the MTL patients in terms of gender (4 women), age (mean=59.4), education (mean=14.6), and verbal IQ (mean=111.8).

All participants provided informed consent in accordance with the Institutional Review Board of VA Boston Healthcare System.

2.2. Procedure

Participants were asked to imagine and describe in as much detail as possible events that might occur a few years in the future. They were asked to describe five events from their own perspective (Self condition; e.g., Imagine attending a Fourth of July cookout a few

years from now) and five events from the perspective of a “familiar other” (Other condition; e.g., Imagine your house cleaner getting a surprise visit from an old friend a few years from now)[1]. Participants were told not to include themselves in the scenarios imagined in the Other condition. They were asked to describe novel, discrete events, that took no longer than a day to unfold. Participants were allotted 3 minutes to describe each event. No additional probing was provided if participants ended their narrative before this deadline. The Self and Other conditions were administered in separate sessions, with the order of sessions counterbalanced across subjects. Assignment of cues to Self and Other conditions was also counterbalanced across subjects.

The selection of familiar others, to serve as agents for future events in the Other condition, was tailored to each individual participant. Prior to the episodic prospection task, participants were asked to select from a list of potentially familiar others (e.g., your doctor, mayor of your town, a neighbor) five individuals they had encountered either personally or in the media. Close others were not included in the list because of evidence that close relationships are incorporated into the self (Aron, Aron, Tudor, & Nelson, 1991). After completing the episodic prospection task, participants rated the selected familiar others in terms of familiarity using a 7-point Likert scale (1=total stranger; 7=close acquaintance).

2.3 Scoring

Because future events are by nature hypothetical, it is difficult to ascertain with certainty their plausibility. Therefore, the only criterion we placed on future events was that they not entail impossible (i.e. fantastical) elements. No participant generated events that contained such elements. Consequently, all narratives were scored and included in the analysis. All study measures were established prior to data analysis.

2.3.1 Narrative details.—As in our prior work (Race et al., 2011), narratives were scored for internal and external details using an adapted autobiographical interview scoring procedure (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). Each narrative was segmented into distinct details, which were then categorized as either internal or external. A detail was categorized as internal if it referred to the main event described, was specific to space and time, and evoked a sense of personal experiencing. Internal details were further categorized as event, place, time, perceptual, and thought/emotion details. All other details were categorized as external. External details included general semantic details, biographical semantic details (i.e., pertaining to the subject of the narrative, whether self or familiar other), external event details (i.e., pertaining to events other than the main event being described), and other external details, which included repetitions and metacomments. Because of the paucity of general semantic details (all medians = 0, means ranging from 0 to 0.05), this detail type was not formally analyzed. Combining general semantic details with biographical semantic details yielded results identical to the analysis of biographical semantic details in isolation. Scores for each detail type were calculated by averaging the number of details of that type across the five narratives in each condition. Interrater

[1]Seven participants had 4 rather than 5 valid narratives in the Other condition. This was due to experimenter error (1 MTL patient), inclusion of the self in the Other condition (1 vmPFC patient and 4 controls), or selection of an unfamiliar other (1 MTL patient).

reliability was determined by having a second rater score 20% of all narratives. The secondary rater, but not the primary rater, was blind to subject status, in accordance with established scoring procedures (Levine et al., 2002; Verfaellie, Bousquet & Keane, 2014). The intraclass correlation indicated high agreement for internal details (Cronbach's α=.99; range =.82 – .98 for each of the subcategories of internal details), as well as for biographical semantic (α=.96), external event (α=.99) and other external details (α=.92).

2.3.2 Self-referential processing.—In keeping with other studies (Bertossi, Tesini, et al., 2016; Kurczek et al., 2015), narratives in the Self condition were coded for references to self and to other individuals. Self-references were instances in which the first person singular or plural occurred in the subject or object position of a sentence (e.g., I, mine, our, etc.); other-references were instances in which the subject or object of a sentence was one or more other individuals, as specified by proper names, personal roles (e.g., the doctor), and third person pronouns (e.g., she, their, him). Repetitions of self or other references contained in a false start were counted only once (e.g., so, I was of course, I was starving). A self-reference index was calculated by dividing the number of self-references by the total number of (self + other) references (Bertossi, Tesini, et al., 2016; Kurczek et al., 2015).

2.4. Data Analysis

Internal and external details were analyzed separately. Due to the small sample sizes, nonparametric statistics were used when possible. Mann-Whitney U tests were used to compare the detail scores of each patient group to their respective control group. Within-group differences in detail scores as a function of condition (self, other) were analyzed using Wilcoxon signed rank test. To assess whether the effect of condition differed across groups, a self-benefit score, reflecting the difference in performance between the Self and Other condition, was calculated and compared across groups using Mann-Whitney U test. Further, to directly compare the magnitude of the self-benefit in the two patient groups, for each patient the difference in episodic details generated in the Self condition and Other condition was expressed as a z-score with reference to their control group and z-scores of the two patient groups were compared using t-tests. We also implemented a nonparametric approach, whereby we ranked the magnitude of the self-benefit for each patient in relation to their control group, and compared the rank of the two patient groups using Mann-Whitney U test.

The proportion of self-references was compared between each patient group and respective control group using Mann-Whitney U test. As above, to directly compare performance in the two patient groups, patients' use of self-references was expressed with reference to their control group using both z-scores and rank scores.

No part of the study procedures or analyses was pre-registered prior to the research being undertaken. Experimental data are available at DOI 10.17605/OSF.IO/FMSPZ. Ethical restrictions prevent archiving of individual lesion data because CT and MRI scans contain personally identifiable information. This data can be requested from the lead author.

3. Results

3.1 Familiarity of agents selected for the Other condition

Both patients and controls rated the individuals for whom they imagined events in the Other condition as moderately familiar. There were no differences in familiarity ratings between the vmPFC group (median=4.2; mean=4.5) and their controls (median=4.2; mean=4.1; U=52.5, p=.49) or between the MTL group (median=4.5; mean=4.0) and their controls (median=3.6; mean=3.8; U=56, p=.65).

3.2 Event details

3.2.1 Internal details.—Figure 3 presents the mean number of internal details generated in the Self and Other conditions (see also Table 2 for median scores) and Table 3 shows examples of future events generated by the vmPFC patients, MTL patients, and their respective controls in the two conditions. As can be seen, a numerical self-benefit was observed in both control groups (present in 14/16 vmPFC controls and 11/16 MTL controls) as well as in the MTL patients (present in 7/8 patients), but not in the vmPFC patients (effect present in 2/8 patients).

The analysis of vmPFC patients and their controls revealed that vmPFC patients generated fewer internal details than controls in the Self condition (U=19, p=.005, η^2=.32) but not in the Other condition (U=51, p=.45). Examination of the different subtypes of internal details (see Appendix 2) revealed that the group difference in the Self condition was significant for event details (U=26.5, p=.019, η^2=.22) and for thought/emotion details (U=15, p=.002, η^2=.38). The increase in details generated in the Self vs Other condition (i.e., the self-benefit) was smaller in the vmPFC group than in controls (U=22, p=.009, η^2=.28). Importantly, the self-benefit was significant in controls (Z=2.85, p=.004, η^2=.25), but not in vmPFC patients (Z=.981, p=.33). In fact, the number of internal details provided by vmPFC patients was numerically greater in the Other condition than in the Self condition. Although the self-benefit in controls was numerically present for all subtypes of internal details, it was significant only for event details (Z=2.54, p=.011, η^2=.20) and thought/emotion details (Z=2.12, p=.034, η^2=.14).

In a follow up analysis we separately examined the performance of the vmPFC patients with good memory and those with poor memory (see Appendix 3). In contrast to controls, there was no evidence for a self-benefit in either patient group (both Z's<.41), despite the fact that vmPFC patients with good memory provided as many details in the Other condition as did controls.

The analysis of MTL patients and their controls showed that MTL patients produced significantly fewer internal details than did controls in both the Self (U=22, p=.009, η^2=.28) and Other (U=12, p=.001, η^2=.42) conditions, but the self-benefit was significant in both MTL patients (Z=2.31, p=.021, η^2=.33) and controls (Z=2.02, p=.044, η^2=.13). There was no difference in the magnitude of the self-benefit in the two groups (U=61, p=.88). Examination of the different subtypes of internal details (see Appendix 2) revealed that groups differed in their generation of event (U=29.5, p=.032, η^2=.19) and perceptual details (U=28, p=.027, η^2=.20) in the Self condition and of event (U=22, p=.009, η^2=.28), place

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(U=29.5, p=.032, η^2=.19), time (U=18, p=.004, η^2=.35), and thought/emotion (U=17, p=.003, η^2=.35) details in the Other condition.

A direct comparison of the magnitude of the self-benefit in the vmPFC (mean z=−1.05) and MTL patients (mean z=−.03) relative to their respective control group using parametric statistics indicated that the self-benefit was reliably different across the two patient groups (vmPFC mean z=−1.05; MTL mean z=−.03; t(14)=3.25, p=.006, d=1.62). A nonparametric analysis based on the ranking of self-benefit scores for each patient relative to their respective controls yielded similar results (U=12.5, p=.038, η^2=.26).

3.2.2 External details.

—Table 2 also presents the number of semantic biographical, external event, and other external details generated in the Self and Other conditions. There were no significant differences between vmPFC patients and their controls in any of the external detail types in the Self condition (U's≥49.0, p's≥.38). In the Other condition, there were no group differences in semantic biographical or external event details (U's≥48.0, p≥.35), but vmPFC patients generated fewer other external details (repetitions and metacomments) than controls (U=25.5, p=.016, η^2=.23). In controls, the effect of condition was not significant for any external detail type (Z's <1). In vmPFC patients, the effect of condition was significant for other external details only (Z=2.20, p=.028, η^2=.30; other subtypes Z's≤1.27).

The analysis of external details in MTL patients and their controls revealed no significant group differences in any of the external detail types in either the Self (U's≥41.0, p's>.17) or the Other condition (U's ≥47.5, p's ≥.32). Controls generated more external event details in the Self than in the Other condition (Z=2.70, p=.007, η^2=.23), an effect that was also numerically present in MTL patients, albeit nonsignficant (Z=1.47, p=.14). Semantic biographical and other external details were not affected by condition in either group (Z's<1).

3.3 Self-referential processing.

The proportion of self-references was lower in vmPFC patients (median=.53; mean=.56) than in their controls (median=.63, mean=.62), a difference that was marginally significant (U=32, p=.052, η^2=.16). The proportion of self-references in MTL patients (median =.51; mean=.49), was also lower than in their controls (median=.59; mean=.59), a difference that again was marginally significant (U=34, p=.07; η^2=.14). Expressed as z-scores relative to their corresponding control group, the self-reference deficit was of similar magnitude in vmPFC patients (z=−.85) and in MTL patients (z=−.92; t<1). A nonparametric analysis based on the ranking of patients' self-reference scores in relation to their respective control group yielded similar results (U=29, p=.80).

4. Discussion

To gain leverage on the role of vmPFC in future thinking, we assessed how psychological distance impacts the richness of imagined events in patients with vmPFC lesions. Participants generated imagined events about the self and about another person with whom they had some, albeit limited, familiarity. In contrast to controls, vmPFC patients were no

more detailed in their description of simulated events about oneself than about another person, as evidenced by the fact that they provided no more internal details in the Self condition than in the Other condition. This was true both for patients with poor memory, whose performance in the Other condition was impaired, and for patients with good memory, whose performance in the Other condition was normal. These findings suggest that the absence of a self-benefit is not a consequence of poor memory, although memory impacts the ability to construct detailed future thinking more broadly. The absence of a self-benefit in vmPFC patients contrasts with the findings in MTL patients who, like controls, showed a benefit associated with generating scenarios about the self, albeit that their descriptions were impoverished in both conditions. The differential results in the two patient groups cannot be ascribed to greater damage in the relevant brain structure in vmPFC patients compared to MTL patients, as MTL damage was proportionately similar to vmPFC damage (and hippocampal damage was proportionately greater than vmPFC damage).

Several previous studies have demonstrated a lack of detail in the future simulations of vmPFC patients (Bertossi, Aleo, et al., 2016; Bertossi, Tesini, et al., 2016; but see Kurczek et al., 2015), but the present study is the first to demonstrate that this impairment is exacerbated when simulations are relevant to the self. The lack of a self-benefit in episodic prospection in vmPFC patients is consistent with extensive neuroimaging (Denny et al., 2012; Martinelli, Sperduti, & Piolino, 2013; Murray, Debbane, Fox, Bzdok, & Eickhoff, 2015) and lesion evidence (Fellows & Farah, 2007; Marquine et al., 2016; Philippi, Duff, Denburg, Tranel, & Rudrauf, 2012; Schneider & Koenigs, 2017) for the role of vmPFC in processing information relevant to the self. Notably, whereas previous evidence for a selective impairment in processing information pertaining to the self following vmPFC lesions comes from studies of the self-reference effect in memory (Philippi et al., 2012) and decisions about trait knowledge (Marquine et al., 2016), the current study extends to future thinking the range of domains in which such an impairment is apparent.

Neuroimaging research on future thinking has shown that vmPFC engagement depends on the extent to which episodic simulations can draw on pre-existing knowledge structures, with vmPFC mediating the integration of various elements stored in distributed neocortical regions (Benoit et al., 2014). Considering the self-schema as a dominant schema that has pervasive impact, it has been suggested that the mental model of the self, instantiated by vmPFC, supports episodic prospection by framing the search for, and integration of, relevant personal details into a coherent event (D’Argembeau & Mathy, 2011; D’Argembeau et al., 2010).

Based on a meta-analysis of tasks that consistently demonstrate vmPFC activation, Roy and colleagues (Roy, Shohamy, & Wager, 2012) have suggested that there are two distinct anatomical and functional subsystems in vmPFC, albeit with partial anatomical overlap, one involved with the constructing of internal models and the other involved with affect generation. Notably, schema-processing and self-related processing both engage the former subsystem, whereas self-related processing additionally engages the latter. We postulate that it is impairment in the former subsystem that underlies patients’ inability to draw on self-information in the simulation of future events.

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Given the role of vmPFC in the activation of abstract self-knowledge, one might question why in control subjects the Self condition increased the generation of episodic, but not semantic details. That is, in addition to facilitating the retrieval of a specific event and providing details that enrich the event, one might also expect greater incorporation of schematic information relevant to the self. A recent study by Devitt et al. (Devitt, Addis, & Schacter, 2017), however, sheds light on why this may not be the case. Re-analyzing data from a number of different studies, the authors found that the amount of episodic and semantic content within individual narratives is negatively correlated, a finding they interpreted as reflecting a compensatory generation of semantic details when episodic details are low. Thus, although more biographical details may be available in the Self condition, they may not be incorporated in the narratives given that additional specific event (i.e., internal) details are now available. In this context, it is of note that the inability of vmPFC patients to draw on self-knowledge in the simulation of future events was evident not only at the level of internal details; Self-relevance also did not affect the number of semantic biographical details provided, suggesting that the lack of self-benefit is not simply due to an inability to incorporate personal information into specific events, but rather may reflect a broader failure to access self-related information in support of event simulation.

The notion that self-relevance facilitates access to event details may provide an explanation for the contrasting results of our study and those of Bertossi, Tesini, et al. (2016), who found that vmPFC lesions impacted future simulations about the self, close others, and distant others to the same extent. Notably, that study also did not observe a self-benefit in the performance of control subjects. A potentially relevant methodological distinction lies in the fact that Bertossi and colleagues used single word cues as probes, which pose a higher demand on event *construction*, whereas the current study used structured event cues, and as such, may have been more sensitive to differences in event *elaboration*. We speculate that the opportunity to draw on self-schema information becomes pertinent primarily once a personally relevant event has been constructed (see also Addis, Wong, & Schacter, 2007).

Focusing on the narrative quality of future simulations, McCormick and colleagues (McCormick, Ciaramelli, De Luca, & Maguire, 2018) recently characterized the mental simulations of vmPFC patients as momentary snapshots, lacking a sense of dynamic unfolding. They linked this impairment to a deficit in processing schema-related information, in that schemas may provide the “backbone” for the construction of events extending in time (e.g., the typical unfolding of a dinner at a restaurant). Such an interpretation provides a potential explanation for the fact that vmPFC patients (with intact memory) in Kurczek et al. (2015) provided narratives that were as detailed as those of controls. Those narratives, unlike those in Bertossi, Tesini, et al. (2016) and in the present study, focused only on a circumscribed fragment of an evolving event. It is less clear how this interpretation can account for the finding in the current study that vmPFC patients with intact memory were not impaired when generating scenarios about another person. However, it is possible that only event probes that strongly activate a schema benefit from the contribution of vmPFC to the dynamic unfolding of an event. Our scenarios were not selected to require activation of a well-established schema, and this may explain the absence of significant impairment in the Other condition. A direct manipulation of demands on schema activation is necessary to shed further light on the viability of this interpretation.

In contrast to patients with vmPFC lesions, those with MTL lesions demonstrated a self-benefit of equivalent magnitude to that observed in controls, suggesting that the ability to leverage knowledge about the self in the service of constructing detailed mental simulations does not critically depend on the MTL. Our findings accord with neuroimaging data from Szpunar and colleagues (2007) who observed greater recruitment of vmPFC but equivalent hippocampal recruitment when comparing future thinking about the self and a familiar individual (Bill Clinton). It should be noted that in another study examining counterfactual simulations (De Brigard, Spreng, Mitchell, & Schacter, 2015), hippocampal activation was greater in a Self than Other condition, but this may reflect the intentional or incidental retrieval of the actual autobiographical event in the process of constructing a counterfactual outcome (see Rabin & Rosenbaum, 2012, for a similar interpretation of modulation of hippocampal activity by familiarity in the context of a theory of mind task).

Seen in the context of an overall reduction in event detail, MTL patients' ability to leverage self-relevant information in the service of future thinking provides further support for the notion that semantic as well as episodic processes support future thinking (Irish & Piguet, 2013; Szpunar, Spreng, & Schacter, 2014). Evidence suggests that MTL lesions leave unaffected the ability to retrieve abstract forms of self-knowledge such as autobiographical facts that are devoid of spatiotemporal information (Grilli & Verfaellie, 2016) and traits and roles (Grilli & Verfaellie, 2014). Thus, activation of the self-schema may have facilitated, for MTL patients as well as for controls, access to such personal knowledge as a source of details that can be incorporated in simulated events – a process shown to be mediated by functional connectivity between vmPFC and content-specific posterior brain regions (Benoit et al., 2014; also see McCormick, Moscovitch, Valiante, Cohn, & McAndrews, 2018, for similar findings in the context of autobiographical memory). Yet, regardless of psychological distance, MTL patients' simulations were impoverished. On the one hand, this may reflect difficulty retrieving episodic details that are required to imagine any future event, whether pertaining to the self or to another person (Schacter & Addis, 2007; Schacter, Addis, & Szpunar, 2017). On the other hand, both of these conditions make demands on relational processes, as details derived from semantic and/or episodic memory need to be combined in novel ways to generate a fictitious event (Schacter & Addis, 2007, 2009). Similarly, both conditions require the construction of spatially coherent scenes within which event details can be incorporated (Hassabis & Maguire, 2007; Maguire & Mullally, 2013). Evidence suggests that associative binding in the service of future thinking (Romero & Moscovitch, 2012) and scene construction (Hassabis, Kumaran, Vann, et al., 2007; Mullally, Intraub, & Maguire, 2012; but see Kim, Dede, Hopkins, & Squire, 2015) are both impaired following MTL lesions.

The contrasting effects of a psychological distance manipulation on future thinking in patients with vmPFC versus MTL lesions may shed light on the findings of Kwan and colleagues (Kwan, Kurczek, & Rosenbaum, 2016) who compared the performance of patients with MTL amnesia when imagining future events in response to personally meaningful cues and to generic cues. Three of five patients showed a benefit associated with self-related cues, in line with the current findings, but the other two did not. Kwan et al. (2016) postulated that the lack of benefit in these two patients might be a consequence of the extent of lesion or memory impairment. Notably, of the two patients who did not show a

benefit, one had a lesion that extended into ventral frontal cortex; for the other patient, no lesion information was available. Thus, an interpretation of their findings suggested by the current study is that involvement of vmPFC is responsible for the lack of self-benefit.

A limitation of the present study is that we did not collect information about the date of simulated events. We asked participants to construct events "a few years" in the future, but participants may have interpreted this in different ways, thus adding noise to the data. However, it seems unlikely that interpretation of the temporal frame would have systematically differed across groups. "A few years" might have different meaning depending on one's age, but ages were closely matched across patients and their respective control groups. More importantly, even acknowledging that individuals may have a preferred interpretation of the temporal frame, there is no reason to think that such an interpretation would differ for the Self and Other conditions. Thus, the critical finding concerning the self-benefit would not be confounded by variable interpretations of the time frame.

Our findings also speak to the difficulty of interpreting the use of personal pronouns in fictitious event narratives. Kurczek et al. (2015) found that patients with vmPFC lesions, but not MTL lesions, used fewer personal pronouns in their narratives, a finding which they interpreted as evidence for the notion that vmPFC lesions lead to impaired self-related processing. The finding of a reduced self-reference index in the vmPFC patients in our study is in agreement with their results (but see Bertossi, Tesini, et al., 2016). Yet, we found that patients with MTL lesions also used fewer personal pronouns, despite being able to use self-related information in service of mental simulation, as evidenced by their intact self-benefit. Reasons for the discrepancy in findings in the MTL patients in our study and in Kurzcek et al. (2015) are unclear. Notably, however, the results of the present study suggest that a reduced use of personal pronouns does not necessarily reflect a failure to exploit self-related information in the service of future thinking.

In summary, the present study manipulated psychological distance as a means to illuminate the contribution of vmPFC to future thinking. Patients with vmPFC lesions were no more detailed in their simulations pertaining to the self than to others. By contrast, patients with MTL lesions showed a normal self-benefit. These findings accord with neuroimaging work implicating vmPFC in self-related processing and elucidate the nature of the contribution of vmPFC to future thinking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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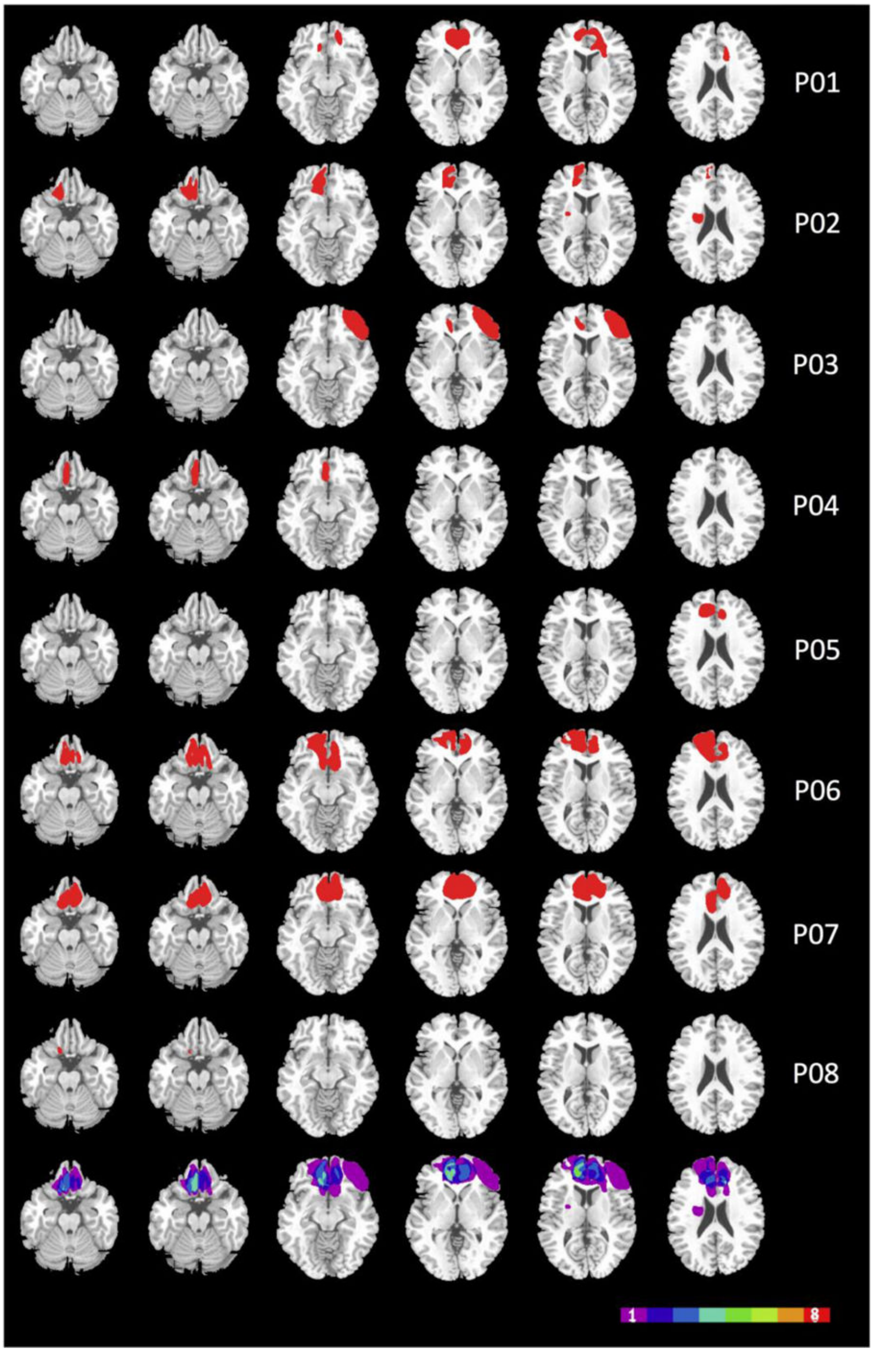

Figure 1:
Location of brain lesions in ventromedial prefrontal cortex (vmPFC) patients and lesion overlap across patients. Lesions are projected on the same six axial slices of the Montreal Neurological Institute brain, according to radiological convention (i.e., the left side of the brain is displayed on the right side of the image). The color bar indicates the number of overlapping lesions.

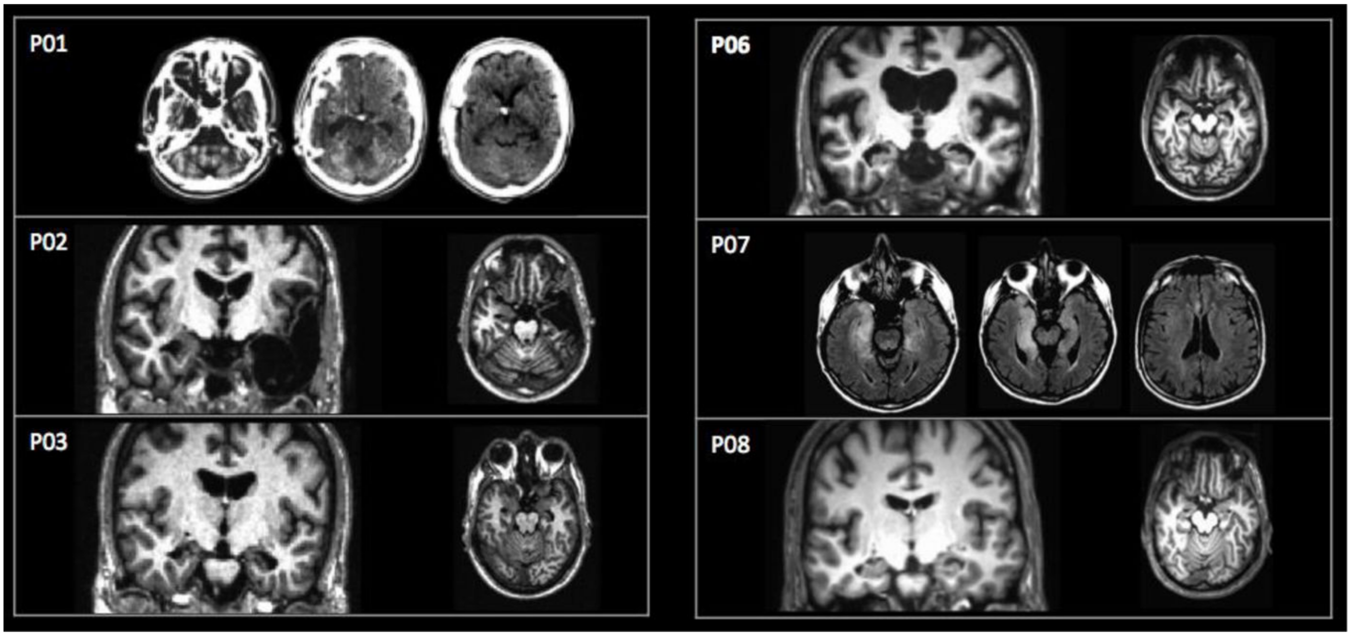

Figure 2.

CT and MRI scans, displayed according to radiological convention, depicting medial temporal lobe (MTL) lesions for six of the eight amnesic patients (see Methods). CT scans show lesion location for P01. T1-weighted MRI images show lesions for P02, P03, P06, and P08 in the coronal and axial plane, and T2-FLAIR images show lesion location for P07 in the axial plane.

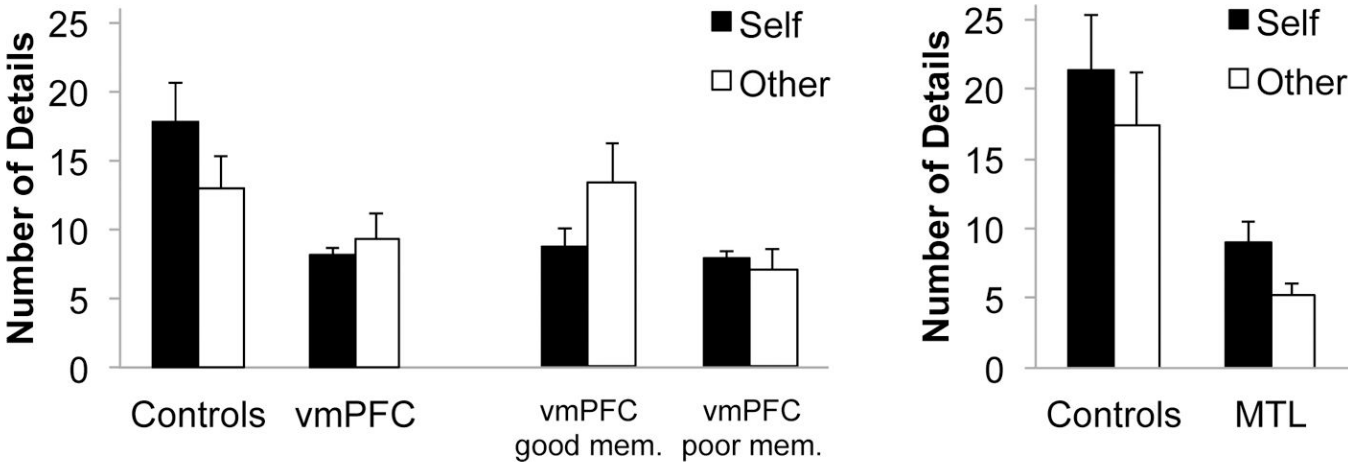

Figure 3.
Mean number of internal details generated in the Self and Other conditions by patients with ventromedial prefrontal cortex (vmPFC) lesions and controls, as well as by patients with medial temporal lobe (MTL) lesions and controls. vmPFC patients are also subdivided into subgroups according to memory performance. Error bars indicate SEM.

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Table 1.

Demographic and neuropsychological characteristics of participants with lesions of ventromedial prefrontal cortex (vmPFC) and medial temporal lobe (MTL) lesions.

	Etiology	Age	Edu	WAIS III		WMS III			BNT	COWA	LNS
				VIQ	WMI	GM	VD	AD			
vmPFC group											
P01	ACoA aneurysm	74	12	92	90	72	88	58	N/A	.11	0
P02	ACoA aneurysm	69	16	112	109	111	103	111	−1.2	−.58	.33
P03	ACoA aneurysm	59	16	106	104	111	118	105	−.33	.29	.67
P04	ACoA aneurysm	68	16	118	109	91	100	89	.78	.58	.67
P05	ACoA aneurysm	64	13	97	88	63	68	58	.11	−.77	−1.33
P06	ACoA aneurysm	35	16	110	106	83	75	89	.04	−1.85	.67
P07	ACoA aneurysm	65	12	97	99	62	62	64	−.74	−.85	−.67
P08	ACoA aneurysm	23	12	93	92	49	68	46	−1.4	.05	−.33
MTL Group											
P01	Hypoxic-ischemic	65	12	88	75	52	56	55	−1.3	−1.1	−2
P02	Status epilepticus + left temp. lobectomy	51	16	93	94	49	53	52	−4.6	−.96	−1
P03	Hypoxic-ischemic	59	14	106	115	59	72	52	.54	−.78	1.33
P04	Hypoxic-ischemic	63	17	131	126	86	78	86	1.3	.03	1.33
P05	Hypoxic-ischemic	65	16	100	88	86	78	83	−.33	.56	−.67
P06	Hypoxic-ischemic	47	12	103	95	59	68	55	.13	−1.5	−.33
P07	Encephalitis	73	13	99	104	49	56	58	−.11	−.5	.33
P08	Stroke	50	20	111	99	60	65	58	1.02	2.1	−.33

Note. Age, age in years; Edu, education in years; WAIS-III, Wechsler Adult Intelligence Scale-III (Wechsler, 1997a); WMS-III, Wechsler Memory Scale-III (Wechsler, 1997b); VIQ, verbal IQ; WMI, working memory index; GM, general memory; VD, visual delayed; AD, auditory delayed; BNT, Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) z-score; COWA, Controlled Word Association Test (Benton & Hamsher, 1989) z-score; LNS, Letter-Number Sequencing z-score.

Table 2.

Number of details provided by patients and their respective control group in the Self and Other conditions.

Group	Self					Other				
	Internal	Semantic Fact	General Semantic	External Event	Other External	Internal	Semantic Fact	General Semantic	External Event	Other External
vmPFC Controls										
Median	14.4	1.7	0	0.2	1.8	10.0	1.5	0	0.1	2.0
Mean	17.9	2.3	0	0.7	2.2	13.0	2.2	0	0.8	2.1
SD	11.2	2.5	0	1.2	1.8	9.1	3.0	0	1.7	1.1
vmPFC Patients										
Median	8.1	1.5	0	0.0	1.6	8.5	1.1	0	0.0	0.9
Mean	8.2	2.1	0	0.3	2.1	9.4	1.2	0	0.1	1.2
SD	1.6	2.2	0	0.4	1.6	4.9	0.9	0	0.2	0.7
MTL Controls										
Median	15.3	3.2	0	0.6	2.2	11.8	3.2	0	0.2	1.6
Mean	21.3	4.2	0.1	1.3	2.6	17.4	3.8	0.1	0.3	3.0
SD	15.6	3.4	0.2	1.8	1.8	14.9	3.7	0.1	0.4	3.6
MTL Patients										
Median	8.0	1.4	0	0.2	2.4	4.9	1.1	0	0.0	2.5
Mean	9.0	2.4	0	0.8	3.0	5.2	2.3	0	0.2	3.3
SD	4.3	2.9	0.1	1.0	2.4	2.4	2.4	0.1	0.3	3.1

Note. external details comprise repetitions and metacomments. vmPFC=ventromedial prefrontal cortex; MTL=medial temporal lobes.

Table 3.

Examples of narratives generated by vmPFC patients, MTL patients and their respective controls in the Self and Other conditions.

Self condition	
vmPFC patient	vmPFC control
This power outage most unfortunately occurred in late December and it was snowing outside. So we were informed by management that we had to leave the building. So we began our hike down 32 floors and then fortunately, there's a Marriot hotel close by, so they were able to trek us all over there and park us until they could get someone in to repair the heating system. You know, to sort of make up for the inconvenience, they did treat us all to a little cognac. And then we went back and tucked up waiting for our room to get warm again.	This is a really bad storm and they warned everybody that there's a good possibility the power will go out. So I went out and stocked up on essentials for the power outage. This is at my house and it's just us and the neighbors pooling our resources, in case we got to hang out during the power outage. It would be better to just hang out with other people. The power went out and we had firewood, so we lit a big fire in the fireplace, broke out the candles, broke out the popcorn and chips, and just waited for the power to come on. It was really no big deal. I wasn't anxious about it or anything. I just figured I'd make the best of it and get through it as best as we could.
MTL patient	MTL control
Ok, not too dissimilar to real life. Up in New Hampshire, way in on a dirt road on a lake. We lose power, lose heat. The fireplace is going to keep the guests warm. Cooking on the grill, lots of wine. Close friends are there for a New Year's Eve party. Lots of laughs when the power goes out.	I'm home and it's the middle of the day. I'm with family, and worried about how long it's going to last because it's very cold. And thankfully, I have a lot of blankets to wrap around myself and relatives as well. And the phone still works, so at least we can keep in touch with different people, to know what's going on. And they can offer any help because they live in a different area. They brought over food because it lasted at least a few hours or whatever. So and because it was winter, we didn't have to worry about too much food going bad from the refrigerator. You just put it out either out in the yard in a bag or something like that to keep it from going bad. And we put a blanket over the dog and cat, so they wouldn't get sick or too cold. It was ok, we survived.
Other condition	
vmPFC patient (other=clergy)	vmPFC control (other=mailman)
Father is turning, let's say the major birthday is 70. He's having a party. The parishioners of his parish gave him a party, a surprise party, at the church hall. They also invited (people) from other parishes that he used to be pastor of. So, he is very happy to see old friends and new friends, and a bit embarrassed, and a bit taken by surprise. But he's also appreciative that people would think that highly of him to do something like that. He has to give a little speech and tell his jokes, because that's what he's good at.	We'll say it is his 30th birthday and his girlfriend decides to throw him a party at her house. So he goes to the girlfriend's house and his friends are there, some of his coworkers, his parents, his siblings. He's eating and drinking and dancing; having a good time. And he is happy. It's his 30th birthday and he's happy. Then he stays for a few hours and then he leaves.
MTL patient (other=clergy)	MTL control (other=mailman)
He would be, I would say 70 years old. It's in Hamden at the church, I'll say church hall or church basement, whichever you want to call it. And there's a lot of people there, a lot of older people there also, naturally. And he being of the popular situation, being from North Haven and of Hamden, and preaching at both churches, being of the popular persuasion, I could see that. And aside from that, I really don't see that much else.	Well, it's his 60th birthday celebration and his birthday is around Thanksgiving time, and they decided – it was a time when the family would get together. They decided that it would be a great time also to celebrate his birthday and they had all of the kids, the grandkids, and even a couple great-grandkids. The mailman has been doing his job with the postal service for over 30 years. And his family, this is such a special celebration, not only with Thanksgiving festivities but also they made beautiful decorations in honor of his birthday. He just felt so honored and so pleased and so special, just as he's been told he is. But he really was able to feel that. And they had this collage of pictures of all the children, and grandchildren and great-grandchildren. Just a collection of pictures that they put on a big cardboard and had everybody sign as they came in. And it just was a joyous time and he just was so pleased and so honored.

Note. vmPFC=ventromedial prefrontal cortex; MTL=medial temporal lobes.