The role of ventromedial prefrontal cortex in reward valuation and future thinking during intertemporal choice

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Abstract

Intertemporal choices require trade-offs between short-term and long-term outcomes. Ventromedial prefrontal cortex (vmPFC) damage causes steep discounting of future rewards (delay discounting; DD) and impoverished episodic future thinking (EFT). The role of vmPFC in reward valuation, EFT, and their interaction during intertemporal choice is still unclear. Here, twelve patients with lesions to vmPFC and forty-one healthy controls chose between smaller-immediate and larger-delayed rewards while we manipulated reward magnitude and the availability of EFT cues. In the EFT condition, participants imagined personal events to occur at the delays associated with the larger-delayed rewards. We found that DD was steeper in vmPFC patients compared to controls, and not modulated by reward magnitude. However, EFT cues downregulated DD in vmPFC patients as well as controls. These findings indicate that vmPFC integrity is critical for the valuation of (future) rewards, but not to instill EFT in intertemporal choice.

Keywords: delay discounting, ventromedial prefrontal cortex, episodic future thinking, decision making, reward.

Introduction

Choices are often intertemporal, requiring trade-offs between short-term and long-term outcomes. Human and non-human animals tend to prefer smaller-immediate over larger-delayed rewards (Green and Myerson, 2004; Rudebeck et al., 2006). This phenomenon reflects delay discounting (DD), the decrease in subjective value of a reward as the delay until its receipt increases. Several clinical conditions, such as drug addiction and obesity, are associated with steep DD (Bickel et al., 2014), a disproportionate prioritization of immediate gratification associated with poor self-control and impulsivity. The neural mechanisms governing DD and its adaptive modulation are thus of theoretical and clinical relevance.

The ventromedial prefrontal cortex (vmPFC) is causally implicated in intertemporal choice. Indeed, patients with damage to the vmPFC (Sellitto et al., 2010; Peters and D'Esposito, 2016; Yu et al., 2020; but see Fellows and Farah, 2005), and animals with lesions in homologous regions (Rudebeck et al., 2006), show abnormally steep DD. The specific role played by vmPFC in DD, however, is still debated. According to a prominent model of intertemporal choice (Hare et al., 2009; Figner et al., 2010; Peters and Büchel, 2011), vmPFC is engaged in reward valuation and integrates different outcome attributes (e.g., amounts, delays), whereas lateral prefrontal cortex modulates vmPFC subjective value signals to promote self-control and future-oriented choice.

In separate work, Peters and Büchel (2010; see also Benoit et al., 2011) have shown that cues to imagine personal future events (episodic future thinking, EFT; Suddendorf and Corballis, 1997; Atance and O'Neill, 2001) during intertemporal choices reduce DD, and the DD reduction relates to functional coupling of medial prefrontal regions and the hippocampus, and to the vividness of imagined events. This finding points to prospection as another component process of DD (Peters and Büchel, 2011). Indeed, EFT effects on DD were not (Palombo et al., 2015) or were inconsistently (Kwan et al., 2015) detected in amnesic patients

with medial temporal lobe (MTL) lesions, in line with the evidence that MTLs patients cannot imagine detail-rich future events (Race et al., 2011).

In addition to its role in reward valuation (Bartra et al., 2013), the vmPFC is also a crucial substrate of prospection (Schacter et al., 2012), and, accordingly, vmPFC patients are impaired in EFT (Bertossi et al., 2016a,b; 2017; Ciaramelli et al., 2020). **Although MTL patients are as well, the nature of the EFT impairment is thought to be different in each case. Whereas constructed experience in hippocampal patients is mainly devoid of spatial references, that of vmPFC patients also lacks relevant contents and sensory details, suggesting that vmPFC plays a more general (upstream) role in event construction (De Luca et al., 2018). McCormick et al. (2018), therefore, have proposed that vmPFC initiates (future) event construction by activating schematic knowledge (e.g., about the self, lifetime periods) that drives the collection of relevant individual details, which the hippocampus then assembles into spatially coherent scenes (see also Ciaramelli et al., 2019; D'Argembeau, 2020; Moscovitch et al., 2016; Ghosh et al., 2014). Consistent with this proposal, vmPFC (but not MTL) patients are particularly impaired at imagining self-related (as opposed to other-related) future events, suggesting they fail to activate schematic self-knowledge that favours the collection of individual details for EFT (Verfaellie et al., 2019; D'Argembeau and Mathy, 2011).** DD, therefore, could be causally linked to vmPFC through prospection, as well as through its role in reward valuation.

To investigate the specific contributions of vmPFC to both the reward valuation and prospection components of DD, we compared the effects of reward magnitude and EFT on DD on patients with vmPFC damage with their effects on healthy controls. Twelve vmPFC patients (see Figure 1 for the extent and overlap of vmPFC patients' brain lesions) and forty-one healthy controls chose between smaller-immediate and larger-delayed rewards while we manipulated reward magnitude (small magnitude: €80/$100; large magnitude: €1500/$2000) and the

availability of EFT cues during intertemporal choices. In the EFT condition, participants were cued to imagine personal events to occur at the delays associated with the larger-delayed rewards (see Figure 2 for an example trial).

A magnitude effect is consistently observed such that people discount larger rewards less steeply than smaller ones (Green et al., 1997). This effect has been ascribed to self-control mechanisms supported by the lateral prefrontal cortex (e.g., Ballard et al., 2017). However, impaired reward valuation following vmPFC damage should hinder the differential valuation of large vs. small rewards, and prevent the implementation of self-control when large rewards are at stake**. Thus, we predict, in addition to steep DD, a smaller magnitude effect in vmPFC patients compared to healthy controls.** Concerning prospection, the involvement of vmPFC in EFT (Bertossi et al., 2016a,b) would lead to the prediction of a reduced EFT effect on DD in vmPFC patients, similar to what is observed in MTL patients. However, since vmPFC (unlike MTL) patients' EFT impairment is attributable to a failure in strategically activating self-knowledge structures that drive EFT (e.g., self schema, personal goals; Ghosh et al., 2014), the provision of cues relevant to one's personal future should externally trigger EFT construction in these patients, enabling its influence on intertemporal choice. Thus, we predict a preserved EFT effect in vmPFC patients.

Figure 1. Location and overlap of brain lesions. The panel shows the lesions of the twelve patients with vmPFC damage projected on the same eight axial slices and on the mesial view of the standard Montreal Neurological Institute (MNI) brain. The level of the axial slices is indicated by horizontal lines on the mesial view of the brain, andby *z*-coordinates. The color bar indicates the number of overlapping lesions. Maximal overlap occurs in BAs 11, 10, and 32 of vmPFC. In axial slices, the left hemisphere is on the left side.

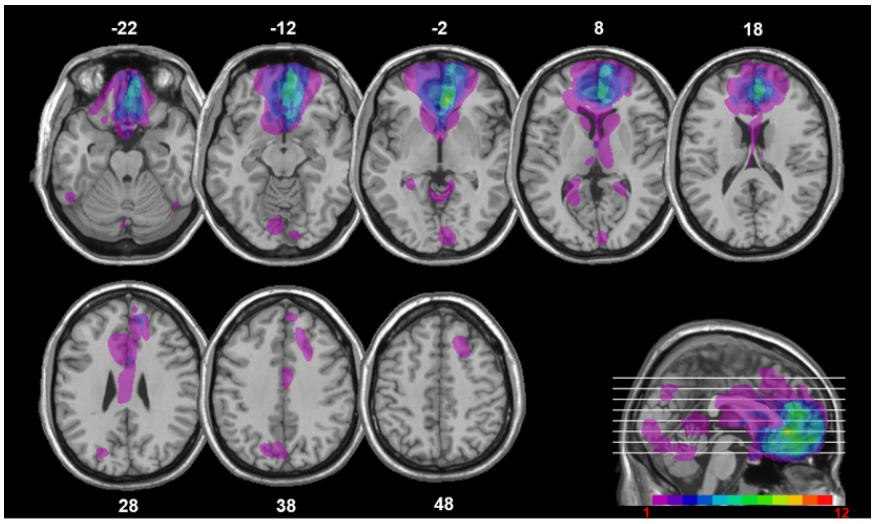
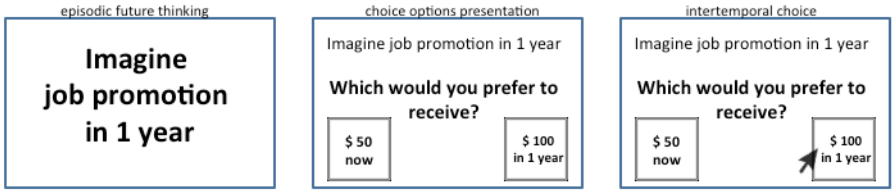


Figure 2. Example of an experimental trial in the EFT condition. Participants were presented with an episodic cue and asked to imagine a personal future experience occurring at a specific delay (e.g., in 1 year). They then were presented with two hypothetical reward amounts and indicated their choice between the smaller-immediate reward and the larger-delayed reward to be received at that delay.



Assessment of DD rates

Results

DD rates. Preliminary fits of the hyperbolic function SV = 1/(1+kD), with SV = subjective value (expressed as a fraction of the delayed amount) and D = delay (in days), to individual participants' data using a nonlinear least-squares algorithm (implemented in Statistica Statsoft) revealed that subjective preferences were not equally well-characterized by hyperbolic functions in the Standard and EFT conditions. This was especially apparent in vmPFC patients in the EFT condition whose discounting curves were not always monotonically decreasing (see Figure 3 and Supplementary Figure 1s for individual patients' discounting curves).

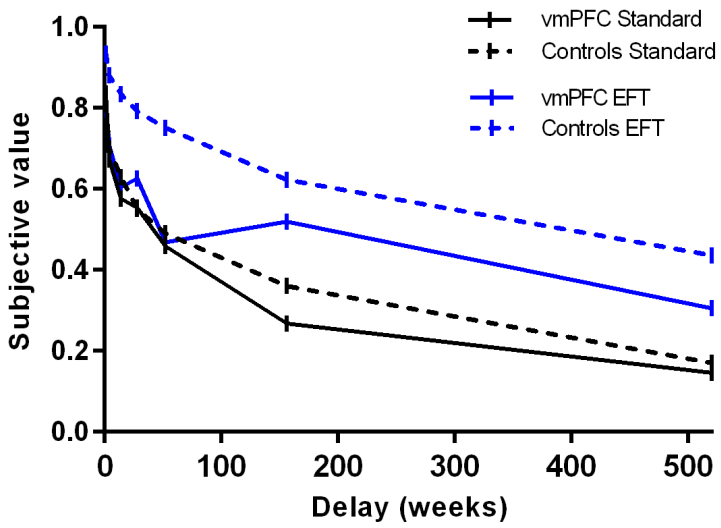


Figure 3. Subjective value as a function of delay by participant group and task condition. Lines represent choices averaged across both reward amounts.

The degree to which participants discounted delayed rewards (DD rate), therefore, was measured using the area under the curve (AuC), a theoretically neutral, normalized measure of DD that does not depend on theoretical models regarding the shape of the discounting curve (Myerson et al., 2001). Figure 4 displays the AuC by participant group and condition, as well

as individual participants' data. An ANOVA on AuCs with Group (vmPFC patients, healthy controls), Condition (Standard, EFT), and Reward magnitude (small, large) as factors revealed an effect of Reward magnitude ($F_{1,51}$= 13.17, p = 0.0007, partial η^2 = 0.20), qualified by a Group x Reward magnitude interaction ($F_{1,51}$ = 9.49, p = 0.003, partial η^2 = 0.16). Fisher post-hoc tests showed that healthy controls discounted large rewards less steeply than small rewards (i.e., magnitude effect; p < 0.0001), whereas vmPFC patients discounted large and small rewards at similar rates (p = 0.76; see Figure 1). Relatedly, vmPFC patients showed steeper DD than controls for the large rewards (p = 0.04), but not for the small rewards (p = 0.67). Crucially, there was a significant effect of Condition ($F_{1,51}$= 54.33, p < 0.0001, partial η^2 = 0.52), indicating that both healthy controls and vmPFC patients had reduced DD rates in the EFT compared to the Standard condition (EFT effect). There were no other significant effects (p > 0.07 in all cases). **In particular, the Group x Condition interaction was not significant ($F_{1,51}$ = 2.18, p = 0.14, partial η^2 = 0.04).**

Because previous work has attributed the magnitude effect to processing in the lateral prefrontal cortex (Ballard et al., 2017, 2018), we re-ran the same ANOVA excluding patients with damage touching the lateral prefrontal cortex (N = 4) to assure that they were not driving our results. We confirmed our findings. Again, the ANOVA yielded a Reward magnitude effect ($F_{1,47}$ = 4.80, p = 0.03, partial η^2 = 0.09), and, importantly, a Group x Reward magnitude interaction that was even stronger than in the original ANOVA ($F_{1,47}$ = 13.32, p = 0.0006, partial η^2 = 0.22), indicating that controls (0.53 vs. 0.39; p < 0.0001), but not vmPFC patients (0.36 vs. 0.40; p = 0.43), discounted large rewards less than small rewards. Note that the magnitude effect ($AuC_{Large\ reward}$ - $AUC_{Small\ reward}$) was even smaller in patients with damage confined to the vmPFC than in patients with additional damage to the lateral prefrontal cortex (-0.04 vs. 0.10; $t_{(10)}$ = -2.60; p = 0.03), confirming that the lack of a magnitude effect in vmPFC patients was not driven by damage extending beyond vmPFC (Figure 1). As in the original ANOVA, there

was a main effect of Condition ($F_{1,47}$ = 33.84, p = 0.000001, partial η^2 = 0.42), **and no Group x Condition interaction ($F_{1,47}$ = 2.89, p = 0.095, partial η^2 = 0.05),** confirming reduced DD rates in the EFT compared to the Standard condition in both vmPFC patients and controls. There were no other significant effects (all ps > 0.23).

A Spearman correlation analysis between the EFT effect ($AuC_{EFT\ Condition}$ - $AuC_{Standard\ Condition}$) and z-scores for internal details attained by vmPFC patients in the EFT section of the Crovitz cue-word test, indicative of the severity of their EFT impairment, gave negative non-significant result ($r_{Spearman}$ = -0.50, p = 0.14).

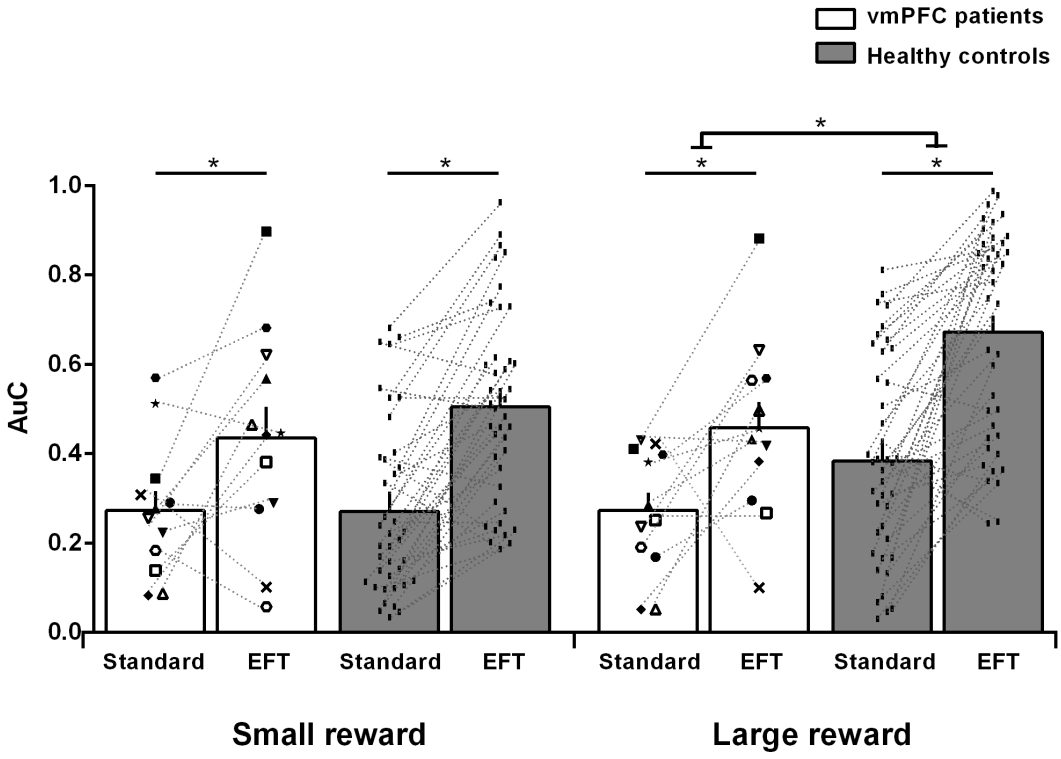


Figure 4. Area under the empirical discounting curve (AuC) by participant group, task condition, and reward magnitude. The figure reports individual participants' data. Empty symbols denote vmPFC patients with brain damage touching the lateral prefrontal cortex.

Consistency of preference. One possible reason for the poor fit of the hyperbolic function to vmPFC patients' discounting data in the EFT condition is that the data were not monotonically decreasing (Figure 3). To directly assess this possibility, we counted the number of "inconsistent choices", i.e., data points in which the subjective value of a future outcome

(amount = R) at a given delay (R_2) was greater than that at the preceding delay (R_1) by more than 10% of the amount of the future outcome (i.e., $R_2 > R_1 + R/10$, as recommended by Johnson and Bickel, 2008; Sellitto et al., 2010). The mean number of inconsistent choices was very low in both vmPFC patients (Standard condition: 0.75, EFT condition: 1.12) and healthy controls (Standard condition: 0.94, EFT condition: 0.61). An ANOVA with Group, Condition, and Reward magnitude as factors revealed a significant Group X Condition interaction ($F_{1,51} = 5.01$, $p = 0.03$, partial $\eta^2 = 0.09$). Post hoc tests indicated that whereas in the Standard condition the number of inconsistent choices in vmPFC patients did not differ from that of healthy controls ($p = 0.31$), replicating previous findings (as in Sellitto et al., 2010), in the EFT condition vmPFC patients showed more inconsistent choices than controls ($p = 0.007$). There were no other significant effects (all ps > 0.13).

Discussion

The present study investigated the effect of vmPFC damage on DD and its responsivity to reward magnitude and cues to imagine personal future events. Three main findings emerged. Whereas healthy controls showed lower DD rates for large compared to small rewards (magnitude effect), vmPFC patients' DD was not modulated by reward magnitude, and was abnormally steep for large rewards. By contrast, external cues for EFT effectively decreased DD in vmPFC patients as well as controls (EFT effect), despite the patients' poor EFT abilities.

Let us first consider the magnitude effect. The tendency to be more likely to choose the delayed option when decisions involve large rewards has been related to self-control mechanisms supported by the lateral prefrontal cortex. This region is more engaged during intertemporal choices between large and small rewards (Ballard et al., 2017), and transient disruption of its activity reduces the magnitude effect (Ballard et al., 2018). Our finding that the magnitude effect is absent in vmPFC patients points to the vmPFC as another crucial substrate of this effect, and makes contact with previous evidence of impaired sensitivity to

magnitude following vmPFC damage (Peters and D'Esposito, 2016). These findings support current models of vmPFC as crucially involved in reward valuation during intertemporal choice (Hare et al., 2009; Figner et al., 2010; Peters and Büchel, 2011). We propose that an impaired reward valuation system impeded the (differential) assessment of the utility of large vs. small rewards, interfering with the normal triggering of self-control by the lateral prefrontal cortex for rewards of high perceived value (di Pellegrino et al., 2007; Ballard et al., 2018).

In the present study, steep DD in vmPFC patients was observed only on choice trials with large rewards, on which greater self-control (shallower discounting) was observed in controls than in patients, **consistent with Peters and D'Esposito's (2016) view that balanced intertemporal choice relies on vmPFC integrity and crosstalk with the lateral prefrontal cortex.** We note that previous studies observed steep DD in vmPFC patients even using reward amounts similar in size to our small reward (Sellitto et al., 2010; Peters and D'Esposito, 2016). The studies, however, had methodological differences from the present effort. Here we studied DD by sampling delays as long as 10 years, whereas previous studies employed much shorter delays (1 year in Sellitto et al., 2010; 60 days in Peters and D'Esposito, 2016), which likely changed baseline levels of discounting, as shown by the fact that the AuC scores of the healthy controls in the present study were lower than those in previous studies. However, the higher baseline rates of discounting the small rewards in the present study, if anything, should have favored the detection of reductions in DD rates with rewards of greater magnitude, and yet no such modulation was observed in vmPFC patients.

Despite being steep at baseline and unresponsive to the amount of reward, vmPFC patients' DD was normally downregulated by cues to imagine the personal future. This finding indicates that vmPFC integrity is not necessary to instill prospection in intertemporal choice with EFT cues. In healthy individuals, EFT is thought to reduce DD by promoting self-projection into vivid future experiences, boosting the value of future payoffs (Boyer, 2008). As

expected, the EFT effect is not reliably observed in MTL patients (Palombo et al., 2015; Kwan et al., 2015), who cannot imagine detail-rich future events (Race et al., 2011). Considering that EFT is also heavily compromised in vmPFC patients (Bertossi et al., 2016a,b; 2017), how might EFT cues exert influence on their choices? EFT is supported by a distributed neural network, including vmPFC and the hippocampus (Schacter et al., 2012), within which different nodes contribute uniquely to the dynamics of EFT construction. **In particular, vmPFC is thought to initiate endogenously the activation of high-level semantic structures (e.g., schemata; Irish and Piguet, 2013; Ghosh et al., 2014), for example pertaining to the self or one's goals (D'Argembeau and Mathy, 2011), around which the hippocampus then builds detail-rich experiences (McCormick et al., 2018; D'Argembeau, 2020). Consistent with this idea, recent magnetoencephalography studies show synchronized engagement of vmPFC and the hippocampus during both autobiographical memory retrieval and scene construction, with vmPFC activity driving activity in the hippocampus during both the initiation and elaboration of mental events (Barry et al., 2019; McCormick et al., 2020). Similarly, vmPFC patients are not impaired in constructing future events (Kurczek et al., 2015; Verfaellie et al., 2019) or scenes (De Luca et al., 2019) if the task minimizes the need for self-initiation, whereas the deficit persists in MTL patients (Kurczek et al., 2015; McCormick et al., 2017; Verfaellie et al., 2019). We propose, therefore, that subject-specific, self-relevant future cues acted as external triggers of self- and situation-relevant schemata, helping to circumvent vmPFC patients' initiation problems. Their intact MTLs allowed them to construct episodic future events, which were then integrated into intertemporal choice. The same benefit would not be expected, and was not found, in patients with severe episodic amnesia due to extensive MTL lesions (Palombo et al., 2015; Kwan et al., 2015), as their basic deficit in assembling detail-rich experiences cannot be offset by probing semantic structures upstream. An alternative interpretation of the DD**

modulation is that EFT cues simply shifted attention towards the future, or conferred a positive valence to it, as we encouraged positively-valenced EFT. If that were the case, however, one should consistently observe an EFT-induced benefit on DD also in MTLs patients, but this is not the case (Kwan et al., 2015; Palombo et al., 2015).

fMRI evidence has related the EFT effect on DD to the crosstalk between the anterior cingulate cortex (ACC, BA 32) and the hippocampus (Peters and Büchel, 2010). Our findings suggest that the ACC is not necessary to update signal values with the EFT output, as this region was lesioned in our vmPFC patients. Our findings are more compatible with the view that in the EFT (vs. Standard) condition, subjective value computation relied on a more distributed network including, in addition to the ACC, the lateral parietal and posterior cingulate cortex (Peters and Büchel, 2010). The parietal cortex mediates shifts of attention to memories (Cabeza et al., 2008) and across subjective time (Nyberg et al., 2010), and the posterior cingulate cortex is implicated in internally directed cognition and EFT (Schacter et al., 2012). These regions were found to form a valuation sub-system dedicated to delayed rewards (Peters and Büchel, 2009), and may have updated reward value based on EFT, overcoming vmPFC patients' domain-general valuation impairment.

One unexpected finding of our study was that vmPFC patients made more inconsistent choices than controls in the EFT condition, while this did not happen in the Standard condition (as in Sellitto et al., 2010). One possibility is that vmPFC patients failed at integrating optimally the attributes of choice options with yet another aspect of the choice context, namely, the products of EFT. This interpretation is in line with the role of vmPFC in weighting multiple aspects of choice options (Pelletier and Fellows, 2019; Vaidya et al., 2018), and in synthetizing the emergent affective quality of a multi-element situation (Benoit et al., 2014). It will be important to confirm the unanticipated finding of an association between EFT cueing and inconsistent choices in vmPFC patients, and to verify whether it extends to other patient

populations, as this aspect of DD has not previously been explored (Kwan et al., 2015; Palombo et al., 2015).

We end by noting some limitations and future directions of our work. Although all twelve patients had lesions centered in the vmPFC, there was some heterogeneity in lesion location, with brain damage extending to the lateral prefrontal cortex in some cases. Our findings held when analyses were restricted to patients with lesions confined to the vmPFC, but future studies including more patients would help confirm the findings and possibly relate them to specific subregions within vmPFC.

In the present study, the order of task conditions was fixed, with the Standard condition always run first, serving as the baseline. Presenting the EFT condition first runs the risk of carryover effects of EFT into the Standard condition, leading to spurious DD baseline levels. This design has been used in previous studies of brain-damaged patients (Palombo et al., 2015; Kwan et al., 2015), and we deemed it even more suited in vmPFC patients who tend to perseverate. Although the repeated-measures design we chose raises the possibility of practice effects, studies have demonstrated the relative stability of individual discount rates over repeated testing (Ohmura et al., 2006; Harrison and McKay, 2012).

Finally, our interpretation of vmPFC patients' preserved EFT effect as due to the external cueing of semantic structures driving EFT is speculative at this point. However, it is consistent with evidence that vmPFC patients produce few internal (episodic) details but a normal number of external (semantic) details during EFT. It is also consistent with current models of vmPFC that postulate it is involved in the self-initiation of event construction (e.g., McCormick et al., 2018; Ciaramelli et al., 2019; Verfaellie et al., 2019). **Further work should study EFT performance in vmPFC patients under conditions that (externally) promote the selection of self-relevant cues for EFT (as in the present study) or not. In this respect, a study by Kurczek et al. (2015) is worth noting. Unlike previous studies of episodic**

remembering and EFT (e.g., Bertossi et al., 2016; 2017), vmPFC patients were guided to choose themselves a specific moment from an extended past or future event to narrate in detail. Under these experimental procedures, vmPFC patients' (re)constructed experience was as context-rich as that of controls, whereas that of MTLs patients remained impoverished nonetheless (Kurczek et al., 2015).

To conclude, the present findings reveal different mechanisms governing DD behavior and its flexibility, which differentially rely on vmPFC integrity. In addition, they may inform the clinical assessment and management of impulsivity in patients with vmPFC damage or dysfunction, delineating the boundary conditions for short-sighted choice to emerge, and the contextual manipulations that are or are not expected to push the reach of patients' choice into the future.

Materials and methods

Participants

Twelve patients with lesions to vmPFC (8 males; mean age = 57.41 years, SD = 8.20, range = 49-76; mean education = 13.41 years, SD = 3.67; range = 8-20; see Table 1 for individual patients' demographic and clinical data) and 41 healthy controls (35 males; mean age = 61.09 years, SD = 6.58, range = 49-78; mean education = 13.19 years, SD = 2.82, range = 8-20) were recruited at the Centre for Studies and Research in Cognitive Neuroscience, Cesena, Italy, and at Baycrest Health Sciences, Toronto, Canada. Patients were selected on the basis of the location of their lesion evident on magnetic resonance imaging (MRI) or computerized tomography (CT) scans (see Figure 1) and were tested at least 12 months post-lesion (see Supplementary material for additional information on patients' recruitment). The lesions of vmPFC patients resulted from rupture of an aneurysm of the anterior communicating artery (in eleven cases) and from stroke of the anterior cerebral artery (in one case). Lesions were bilateral in ten cases and left-lateralized in the remaining two cases. All participants were screened for

any neurological or psychiatric diagnoses likely to affect cognition or interfere with participation. They gave informed consent to participate in the study, which was approved by the ethical committees of the University of Bologna, the Regional Health Service of Emilia Romagna, Baycrest Health Sciences, and York University, and in line with the Declaration of Helsinki (International Committee of Medical Journal Editors, 1991).

Insert Table 1 about here

Lesion analysis

Individual vmPFC lesions were manually drawn by a highly trained neuroscientist directly on each slice of the normalized T1-weighted template MRI scan from the Montreal Neurological Institute using MRIcro software (Rorden and Brett, 2000), based on the most recent MRI or CT scan available. 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). Included patients had lesions mainly affecting Brodmann areas (BAs) 10, 11, 32, 24, and 25, with the region of maximal overlap occurring in BAs 11 (M = 12.50 cc, SD = 10.79), 10 (M = 5.70 cc, SD = 6.46), and 32 (M = 3.71 cc, SD = 3.64) (Figure 1). Four patients had minimal damage to the lateral prefrontal cortex (BAs 9, 46, 47), but this constituted ~ 5% of their lesion volume, while their vmPFC lesions were on average 10 times larger. Two patients had damage to visual cortex (BAs 17, 18, 19, 37) that constituted ~ 41% and ~ 32% of their lesion volume. These patients did not have visual problems precluding their participation in the study. They attained normal scores on the copy of the Rey-Osterrieth Complex Figure (percentile scores: 66 and 68; Spreen and Strauss, 1998) and on the Wechsler Test of Adult Reading (percentile scores: 55 and 47; Holdnack, 2001), and proved able to inspect and comprehend a practice trial of the DD task (see below).

Cognitive profile

The general cognitive functioning of vmPFC patients was preserved in all cases, and their performance on standardized tests of executive function, short-term memory, and long-term memory was, on average, within the normal range (mean percentile > 5), though weak in some cases, especially with respect to verbal long-term memory (see Table 1 for individual patients' neuropsychological data). Moreover, most of the vmPFC patients showed deficits in episodic remembering and EFT, as assessed with the Galton-Crovitz cue-word test, a long-standing method for eliciting autobiographical memories (Crovitz and Schiffman, 1974), later adapted to the assessment of EFT (Addis et al., 2011; see Supplementary material for a detailed description of the test). vmPFC patients produced fewer internal details than their controls while narrating both past events (mean z = -2.16; SD = 0.83) and future events (mean z = -1.62, SD = 0.80), but the number of external details were within normal limits in both cases (past: mean z = -0.39, SD = 1.25; future: mean z = -0.73, SD = 0.89; Table 2).

Delay discounting task

Participants completed a DD task under Standard and EFT conditions. In the Standard condition, over a series of trials, participants viewed pairs of monetary amounts and were asked to choose between an immediate reward and a larger reward available after a delay. For each of two delayed amounts (small magnitude: €80/$100; large magnitude: €1500/$2000), participants were asked to make a block of six choices at each of seven delays (1 week, 1 month, 3 months, 6 months, 1 year, 3 years, and 10 years before receiving the reward), with the resulting fourteen blocks pertaining to the different reward amounts and delays presented in random order. Thus, participants made 84 choices in total (2 reward amounts x 7 delays x 6 choices).

In each block, the first choice was between the future amount and half that amount to be received immediately. An iterative, adjusting-amount procedure was used in which the

amount of the immediate reward was increased or decreased based on a participant's previous choices, so as to converge on an estimate of the amount of immediate reward that was equivalent in subjective value to the delayed reward (see Kwan et al., 2015). The first adjustment was half of the difference between the immediate and delayed amounts presented on the first trial, with each subsequent adjustment being half of the preceding adjustment, rounded to the nearest €/$. For example, in the condition where a future reward of $2000 could be received in 3 years, the first choice presented to the participants was "$1000 right now or $2000 in 3 years." If the participant chose "$2000 in 3 years," the choice on the second trial would be between "$1500 right now" and "$2000 in 3 years." If the participant then chose "$1500 right now," the choice on the third trial would be "$1250 right now or $2000 in 3 years." Following the sixth and final trial, the subjective value of the delayed reward was estimated as the amount of the immediate reward that would be presented on a seventh trial. Participants were told that the task assessed preferences, and therefore there were no correct or incorrect choices.

The DD task in the EFT condition proceeded as in the Standard condition (i.e., with 2 reward amounts x 7 delays x 6 choices), except that each block of choices was preceded by an EFT cue encouraging participants to imagine vividly a personal future event to occur at that delay (Figure 2). In a preliminary session, participants identified planned or plausible personal future events (e.g., appointments, anniversaries, outings) for each of the seven delays in the discounting task. To minimize the possibility of inducing distress, participants were encouraged to include only emotionally neutral or positive future events. vmPFC patients had greater difficulty generating events in comparison to controls, and, therefore, all participants were allowed to refer to personal calendars and electronic devices.

If participants encountered difficulties providing an event, the experimenter probed with the following questions: "Might there be any events with family or friends that may take place

in < delay >?" or "Is there something you could possibly see yourself doing in < delay > or want to do in < delay >?" Once participants had accessed the relevant event, they described it to the experimenter and labeled it with a short tag. These tags were used as future event cues in the EFT condition. During the cued DD task, upon viewing the EFT cue, participants were instructed to imagine the corresponding personal future event in as much detail as possible, and to press a button when they had the event clearly in mind. The button press triggered the decision-making screen, where participants completed intertemporal choices as in the Standard condition. The event cue remained at the top of the screen until the end of the delay block, to reduce demands on memory.

The Standard, uncued version of the task provided a baseline for measuring the effect of future cueing on DD and was run first. The EFT condition was run at least one month after the Standard condition. The experimental conditions were administered in this fashion to avoid carryover effects of the EFT condition, which would likely contaminate the baseline condition (for a similar approach, see Palombo et al., 2015; Kwan et al., 2015). A growing body of research indicates EFT is an effective strategy to reduce DD (reviewed in Rung and Madden, 2018; Bulley and Schacter, 2020), and, as such, it is expected to have carryover effects. Therefore, participants undergoing an EFT condition first might continue to engage in EFT while making choices in the following Standard condition, especially vmPFC patients who are subject to perseveration.

Assessment of DD rates

Preliminary fits of the hyperbolic function SV = 1/(1+kD), with SV = subjective value (expressed as a fraction of the delayed amount) and D = delay (in days), to individual participants' data using a nonlinear least-squares algorithm (implemented in Statistica Statsoft) revealed that subjective preferences were not equally well-characterized by hyperbolic functions in the Standard and EFT conditions, especially in vmPFC patients, whose discounting

curves in the EFT condition were not always monotonically decreasing (Figure 3 and Supplementary Figure 1s). An ANOVA on R^2 values with Group (vmPFC patients, healthy controls), Condition (Standard, EFT), and Reward magnitude (small, large) as factors confirmed a significant effect of Condition ($F_{1,51} = 7.20$, $p = 0.009$, partial $\eta^2 = 0.12$) reflecting the fact that R^2 values were lower in the EFT condition than in the Standard condition (0.54 vs. 0.64). The Group x Condition interaction, which just failed to reach statistical significance ($F_{1,51} = 3.99$, $p = 0.050$, partial $\eta^2 = 0.07$), suggests that the effect of Condition was driven by vmPFC patients (healthy controls: 0.62 vs. 0.58; vmPFC patients: 0.72 vs. 0.41). No other effects were significant (all ps > 0.09).

Given that subjective preferences were not equally well-characterized by hyperbolic functions in the Standard and EFT conditions across groups, the degree to which participants discounted delayed rewards (DD rate) was quantified using the area under the curve (AuC), a measure of DD that does not depend on theoretical assumptions on the shape of the discounting curve (Myerson et al., 2001). Delays and subjective values were normalized. Each delay was expressed as a proportion of maximum delay (120 months) and subjective values were expressed as a proportion of the delayed values. The normalized delays were then plotted on the *x* axis and the normalized subjective values on the *y* axis as a function of delay to construct a discounting curve. Vertical lines were drawn from each *x* value to the curve, subdividing the area under the curve into a series of trapezoids. The area of each trapezoid was calculated as $(x_2 - x_1)(y_1 + y_2)/2$, where x_1 and x_2 are successive delays, and y_1 and y_2 are the subjective values associated with those delays (Myerson et al., 2001). The AUC is the sum of the areas of all the trapezoids. The AUC varies between 0 (maximally steep discounting) and 1 (no discounting). The smaller the AUC, the steeper the DD, and the more participants were inclined to choose smaller-immediate rewards over larger-delayed rewards.

Statistical analyses

Measures of interest were entered in repeated-measures ANOVAs with Group (vmPFC patients, healthy controls) as the between-subject factor and Condition (Standard, EFT) and Reward magnitude (small, large) as within-subject factors. Post-hoc analyses were conducted with the Fisher test. We report results significant at $p < 0.05$, two-tailed, and partial η^2 as measure of effect size.

Conflict of interest statement

The authors declare no competing financial interests.

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Data availability

Data that support the findings of this study are available at https://doi.org/10.5061/dryad.w3r2280qf

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Table legend

Table 1. (I) = patient tested in Italy; (C) = patient tested in Canada; M = male; F = female; Edu = education; y = years; vmPFC = ventromedial prefrontal cortex; EFT Int = internal details at the Crovitz episodic future thinking task; EFT Ext = external details at the Crovitz episodic future thinking task; PF = Premorbid functioning, based on the Full scale IQ at Wechsler Abbreviated Scale of Intelligence (WAIS–IV; Wechsler, 2008), the Wechsler test of adult reading (WTAR; Holdnack, 2001), and the National Adult Reading Test (NART) (Paolo and Ryan, 1992) for Canadian patients, and on the Raven Standard Progressive Matrices (SPM) for Italian patients (Spinnler and Tognoni, 1987); LF = Letter fluency (Spinnler and Tognoni, 1987; Spreen and Strauss, 1998); DS = Digit span; LL Imm = List learning immediate recall, LL Del = List learning delayed recall, assessed with the Buschke–Fuld Test (Buschke and Fuld, 1974; Spinnler and Tognoni, 1987) in Italian patients, and with the California Verbal Learning Test-II (Woods et al., 2006) in Canadian vmPFC patients; ROCF = Rey-Osterrieth Complex Figure (Spinnler and Tognoni, 1987; Spreen and Strauss, 1998). For PF, LF, DS, LL, and ROCF we report percentile scores. Dashes indicate missing data.

Supplementary materials for

The role of ventromedial prefrontal cortex in reward valuation and future thinking during intertemporal choice

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Materials and methods

Patient recruitment

Patients were recruited at the Centre for Studies and Research in Cognitive Neuroscience, Cesena, Italy, and at Baycrest Health Sciences, Toronto, Canada, between 2015 and 2019. **Patients with relatively restricted lesions to vmPFC are rare, and there are no previous studies on the effect of EFT cueing on DD in these patients. Thus, the number of participants was based on previous studies of DD in vmPFC patients (e.g., Sellitto *et al*., 2010: 7 vmPFC patients, 20 healthy controls; Peters and D'Esposito, 2016: 9 vmPFC patients, 19 healthy controls; Fellows and Farah, 2003: 12 vmPFC patients, 26 healthy controls). A somewhat larger N (= 41) for healthy participants was chosen based on previous behavioral findings where the influence of EFT on DD was found using a group of 30 healthy adults (Peters and Büchel, 2010).**

One of the four Italian patients included in the study had participated in a previous study on uncued DD (Sellitto et al., 2010). All eight Canadian patients had taken part in study on DD and probability discounting (both without cues) conducted shortly before the present experiment (Mok et al., 2021, in press), and their uncued DD data are included in the current Standard condition data. As for EFT, all Italian patients had participated in two EFT studies run between 2013 and 2015 (Bertossi et al., 2016b; Bertossi et al., 2017), whereas all Canadian patients were tested between 2015-2019, with results reported for the first time here (Table 1).

Assessment of EFT

The Galton-Crovitz cue-word test is a long-standing method for eliciting autobiographical memories (Crovitz and Schiffman, 1974), later adapted to the assessment of EFT (Addis et al., 2011). The same general testing and scoring procedures for the cue-word test were followed in each lab. Participants were presented with cue words (9/6 cues per condition in Italy/Canada) and were asked to remember past personal events (up to 5 years ago) and to imagine future personal events (up to 5 years into the future). For 'past' trials, participants were asked to recall personally experienced events at specific times and places. For 'future' trials, participants were asked to imagine specific novel events that they might experience in the future. Remembered/imagined events were to last minutes or hours but not more than a day. Participants recounted the event they had in mind for 3/5 minutes (in Italy/Canada), followed by a general probe encouraging greater usage of details ('Is there anything else you can remember/imagine?').

Narratives were scored using the Autobiographical Interview (see Levine et al., 2002; Addis et al., 2011): for each event, narratives were segmented into distinct details, which were categorized as either internal (referring to specific episodic information about the central event) or external (e.g., semantic information, information unrelated to the central event, metacognitive/editorializing statements). Internal and external details were tallied and averaged across trials. Results for the Italian patients were previously reported in Bertossi et al. (2016b). Results for the Canadian patients (unpublished) are presented in Table 1, and z-scores were calculated based on the mean and standard deviation of a previously reported healthy control group (Kwan et al., 2015).

Results

DD rates-control analysis on cultural effects

We tested whether there were cross-cultural differences in the EFT-driven modulation of DD. We repeated our main ANOVA on AuCs with Group (vmPFC patients, healthy controls), Condition (Standard, EFT), and Reward magnitude (small, large) as factors, this type considering Testing site (Italy, Canada) as an additional factor. **We confirmed our findings, which held across different testing sites. Again, the ANOVA yielded a Reward magnitude effect ($F_{1,49}$ = 12.93, p = 0.0007, partial η^2 = 0.20) and a Group x Reward magnitude interaction ($F_{1,49}$ = 7.97, p = 0.006, partial η^2 = 0.13), indicating that controls (0.53 vs. 0.39; p = 0.001), but not vmPFC patients (0.37 vs. 0.35; p = 0.70), discounted large rewards less than small rewards. Moreover, there was a main effect of Condition ($F_{1,49}$ = 45.84, p = 0.00001, partial η^2 = 0.48), confirming reduced DD rates in the EFT compared to the Standard condition in both vmPFC patients and controls. The Group x Condition interaction was not significant ($F_{1,49}$ = 1.44, p = 0.23, partial η^2 = 0.03). There were no other significant effects (p > 0.11 in all cases) and, in particular, testing site had no effect and did not figure in any significant interaction (p > 0.14 in all cases).**

Supplementary figure

Supplementary figure 1. Subjective value of small and large rewards as a function of delay for individual participants in the Standard and EFT condition.

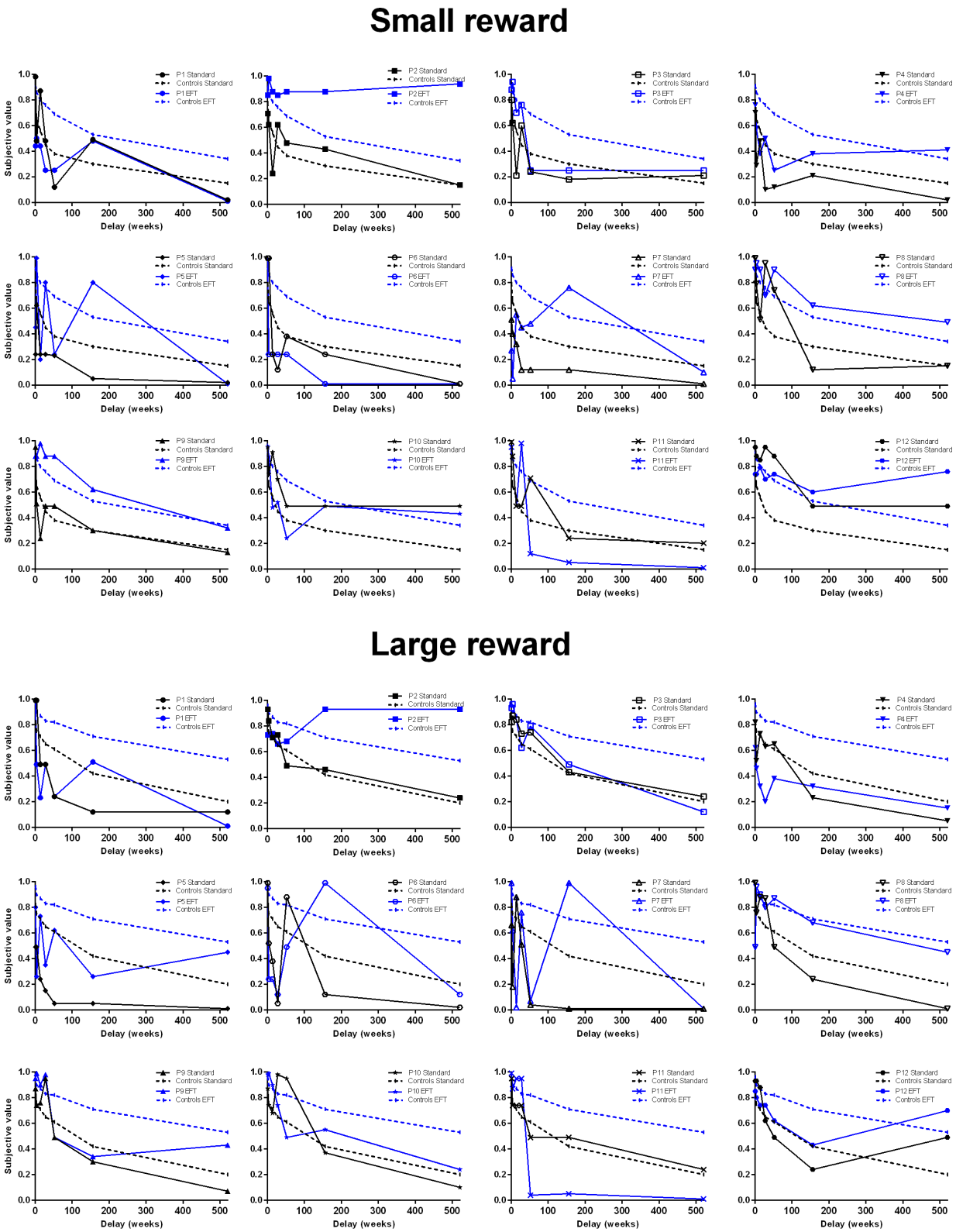

Table 1. vmPFC patients' demographic and clinical data.

vmPFC patient	Age (y)	Edu (y)	Sex (y)	Time since lesion (y)	EFT Int (z score)	EFT Ext (z score)	PF	LF	DS	LL Imm	LL Del	ROCF Copy	ROCF Recall
P1 (I)	55	13	M	4	-1.42	0.58	21%	23%	34%	14%	17%	100%	50%
P2 (I)	46	13	M	7	-1.54	-1.44	38%	7%	49%	12%	8%	100%	41%
P3 (I)	56	8	M	13	-1.43	-0.73	42%	16%	23%	0.43%	3%	25%	2%
P4 (I)	57	8	M	7	-1.57	-0.28	42%	31%	23%	7%	12%	89%	27%
P5 (C)	58	15	F	8	-	-	82%	35%	18%	1%	0.02%	2%	13%
P6 (C)	76	16	F	5	0.38	-0.90	55%	40%	80%	81%	50%	67%	62%
P7 (C)	54	13	F	2	-2.40	-1.76	58%	30%	59%	2%	2-3%	8%	42%
P8 (C)	65	18	M	4	-2.02	-1.03	45%	2%	39%	8%	7%	22%	18%
P9 (C)	56	20	M	4	-2.48	-1.26	47%	-	39%	1%	0.7%	68%	1%
P10 (C)	51	10	M	8	-	-	45%	20%	59%	4%	0.7%	84%	13%
P11 (C)	66	15	F	1	-1.79	-1.42	47%	55%	39%	1%	1%	70%	2%
P12 (C)	49	12	M	5	-1.97	0.92	86%	50%	39%	1%	0.03%	58%	0.7%

Note. (I) = patient tested in Italy; (C) = patient tested in Canada; M = male; F = female; Edu = education; y = years; vmPFC = ventromedial prefrontal cortex; EFT Int = internal details at the Crovitz episodic future thinking task; EFT Ext = external details at the Crovitz episodic future thinking task; PF = Premorbid functioning, based on the Full scale IQ at Wechsler Abbreviated Scale of Intelligence (WAIS–IV; Wechsler, 2008), the Wechsler test of adult reading (WTAR; Holdnack, 2001), and the National Adult Reading Test (NART) (Paolo and Ryan, 1992) for Canadian patients, and on the Raven Standard Progressive Matrices (SPM) for Italian patients (Spinnler and Tognoni, 1987); LF = Letter fluency (Spinnler and Tognoni, 1987; Spreen and Strauss, 1998); DS = Digit span; LL Imm = List learning immediate recall, LL Del = List learning delayed recall, assessed with the Buschke–Fuld Test (Buschke and Fuld, 1974; Spinnler and Tognoni, 1987) in Italian patients, and with the California Verbal Learning Test-II (Woods et al., 2006) in Canadian vmPFC patients; ROCF = Rey-Osterrieth Complex Figure (Spinnler and Tognoni, 1987; Spreen and Strauss, 1998). For PF, LF, DS, LL, and ROCF we report percentile scores. Dashes indicate missing data.