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Neural correlates of event clusters in past and future thoughts: How the brain integrates specific episodes with autobiographical knowledge

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ABSTRACT

When remembering the past or envisioning the future, events often come to mind in organized sequences or stories rather than in isolation from one another. The aim of the present fMRI study was to investigate the neural correlates of such event clusters. Participants were asked to consider pairs of specific past or future events: in one condition, the two events were part of the same event cluster (i.e., they were thematically and/or causally related to each other), whereas in another condition the two events only shared a surface feature (i.e., their location); a third condition was also included, in which the two events were unrelated to each other. The results showed that the processing of past and future events that were part of a same cluster was associated with higher activation in the medial prefrontal cortex (PFC), rostrolateral PFC, and left lateral temporal and parietal regions, compared to the two other conditions. Furthermore, functional connectivity analyses revealed an increased coupling between these cortical regions. These findings suggest that largely similar processes are involved in organizing events in clusters for the past and the future. The medial and rostrolateral PFC might play a pivotal role in mediating the integration of specific events with conceptual autobiographical knowledge 'stored' in more posterior regions. Through this integrative process, this set of brain regions might contribute to the attribution of an overarching meaning to representations of specific past and future events, by contextualizing them with respect to personal goals and general knowledge about one's life story.

Introduction

The capacity to envision events that could happen in the future has attracted a growing interest in the past few years, probably due to the increasing recognition of its importance in the regulation of human behavior (Schacter et al., 2012; Seligman et al., 2013; Suddendorf and Corballis, 2007; Szpunar, 2010). Findings from cognitive, neuropsychological, and neuroimaging research have accumulated rapidly, such that we now have a reasonably clear understanding of the cognitive and neural processes that support the mental representation of individual future events (Schacter et al., 2012; D'Argembeau, 2012; Mullaly and Maguire, 2014). Recent research suggests, however, that future-oriented thinking involves more than imagining isolated events and often consists in considering a set of related events (D'Argembeau and Demblon, 2012; Demblon and D'Argembeau, 2014, in press). The processes involved in linking and organizing imagined events in coherent themes and sequences are not fully understood, and our aim here is to explore the neural bases of knowledge structures that contribute to these event clusters.

Neuroimaging studies have revealed that the recall of past events and the imagination of future events involve a common set of frontal, temporal, and parietal regions (for a recent meta-analysis, see Benoit and Schacter, 2015). Within this core network, regions such as the medial temporal lobe and retrosplenial cortex are thought to support the construction of specific event representations based on episodic details (Schacter and Addis, 2007; Hassabis and Maguire, 2007), whereas other regions (such as the lateral temporal cortex) may store semantic knowledge that provides a coherent scaffolding for constructing such representations (Irish et al., 2012; Irish and Piguet, 2013; Duval et al., 2012). In addition to these brain regions involved in the representation of individual events, other regions within the core network might support the processing of higher-order autobiographical knowledge, which provides a framework for linking imagined events and organizing them in personal themes and stories.

Conway (Conway and Pleydell-Pearce, 2000; Conway, 2005; Conway et al., 2004) has proposed that autobiographical memory is organized in a hierarchy in which specific event representations are part of "general event" representations, which bind a set of specific events on the basis of their thematic similarity and causal relations (see also Barsalou, 1988; Thomsen, 2015). Research has shown that this kind of general autobiographical knowledge is frequently accessed both when recalling specific past events (Haque and Conway, 2001) and when

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imagining specific future events (D'Argembeau and Mathy, 2011). Furthermore, there is evidence that general autobiographical knowledge contributes to organize specific memories and future thoughts in coherent themes and causal sequences, referred to as *event clusters* (Brown and Schopflocher, 1998; Burt et al., 2003; D'Argembeau and Demblon, 2012; Demblon and D'Argembeau, 2014, in press).

The present research aims to investigate the neural basis of such higher-order autobiographical knowledge that contributes to organize specific events in thematic clusters. Previous neuroimaging studies have shown that the representation of general personal information and events involves medial and lateral prefrontal, lateral temporal, posterior cingulate, and inferior parietal cortices (Addis et al., 2004a; Holland et al., 2011; for a meta-analysis, see Martinelli et al., 2013). However, the brain regions that contribute to the organizational function of general autobiographical knowledge (i.e., to link a set of specific events together) have not been investigated. Furthermore, these previous studies focused only on the retrieval of past events, and thus it remains unknown whether the activation of higher-order autobiographical knowledge is supported by the same brain regions during remembering and future thinking.

To investigate these questions, we devised a new task that required participants to simultaneously consider two specific past or future events, and we manipulated the involvement of higher-order autobiographical knowledge by varying the types of relational dimensions linking these two events. Specifically, in one condition the two events were thematically and/or causally related to each other (i.e., they were part of the same event cluster), whereas in another condition the two events shared a surface feature (i.e., their location); a third condition was also included, in which the two events were unrelated to each other. For each pair of events, the participants' task was to determine what relational dimension (if any) links the two events together (i.e., thematic, location, or no relation).

We hypothesized that processing events that are part of the same cluster (compared to events that share a surface feature or that are unrelated to each other) would activate higher-order autobiographical knowledge and recruit brain areas involved in integrating events with such knowledge. A prominent candidate region for this process is the medial prefrontal cortex (mPFC), a region that is activated when processing general autobiographical knowledge (such as general representations of personal information and goals; for recent meta-analyses, see Martinelli et al., 2013; Stawarczyk and D'Argembeau, 2015) and might support the integration of specific experiences with such conceptual knowledge (Brod et al., 2013; Kroes and Fernandez, 2012; Preston and Eichenbaum, 2013; van Kesteren et al., 2012). In addition to the mPFC, rostrolateral regions of the PFC that have been shown to support relational integration and causal reasoning (Barbey and Patterson, 2011; Christoff et al., 2001; Wendelken et al., 2011) could also participate in the processing of event clusters. Finally, given that event clusters rely on higher-order (i.e., more abstract) autobiographical knowledge, we predicted that areas in the temporal and inferior parietal lobes that support semantic processing (Binder and Desai, 2011; Binder et al., 2009; Jefferies, 2013) would also be recruited to a greater extent when participants consider events that are part of the same cluster.

In summary, we expected that, relative to the control tasks (i.e., considering events that share a surface feature or that are unrelated to each other), thinking about past and future events that are part of the same cluster would activate higher-order autobiographical information that provides personal meaning beyond the meaning conveyed by each event taken in isolation, and we predicted that this process would recruit the mPFC, rostrolateral PFC, and lateral temporal and parietal cortices.

Material and methods

Participants

Twenty-eight healthy young adults with no history of neurological or psychiatric disorders took part in the study. Data from five participants were excluded because they did not follow instructions correctly (four participants) or because of poor performance (leaving an insufficient number of correct trials for the analyses; one participant); thus, the analyses were conducted on data from the remaining twenty-three participants (11 females). All of them were native French speakers and ranged in age from 19 to 27 years ($M = 22.5$ years, $SD = 2.4$ years). All participants provided a written informed consent to take part in the study, which was approved by the Ethics Committee of the Medical School of the University of Liège.

Tasks and procedure

Pre-scan session

The day before the scan session, participants took part in a pre-scan interview, the purpose of which was to collect the descriptions of autobiographical past and future specific events which were then used as stimuli during the fMRI session. Participants first received a definition of the notion of 'general event' (i.e., an event extended in time which includes more specific events that are organized in sequences, are causally related to each other, and/or involve the same theme or goal)[1] and some examples of general events were provided (e.g., a vacation in Egypt; the last exam period; moving in a new apartment; learning to drive). Based on this definition, participants were asked to report five general events that might likely happen to them in the next year. For each general event, participants were then asked to imagine three specific events that might likely happen in the context of this general event but would not occur in the same location (i.e., in the same room or area). A definition of specific event (i.e., a particular event occurring in a specific place at a specific time, and lasting a few minutes or hours) and some examples (e.g., passing my driving license test; packing my suitcase to go in Egypt) were provided. The experimenter wrote a short description of each general and specific event that was produced.

Participants were also asked to report five particular locations (i.e., a particular room or area) where they would likely be in the next year. Then, for each location, they imagined three specific events that might occur in this place but that are not part of the same general event (i.e. events that have no relation with each other except that they occur in the same location). Once again, the experimenter wrote a description of each location and specific event that was produced.

The three specific future events that were part of a same general event were used by the experimenter to form three event pairs (i.e. formed by events 1 and 2; events 2 and 3; events 1 and 3), leading to the formation of fifteen pairs of events (3 pairs for each of the five general events reported) that are part of a same event cluster but that occur in different locations. Similarly, the specific future events occurring in the same location were used to form three event pairs, leading to the formation of fifteen pairs of events that occur in the same location but that are not part of a same event cluster. Finally, participants were asked to use the descriptions of the same specific events to assemble fifteen pairs of unrelated events (events that are not part of a same event cluster and do not happen in the same location).

Participants then reproduced exactly the same task with past instead of future events. Thus, they had to recall five general (extended) events that occurred in the past year, five familiar locations where they were regularly in the past year, and three specific memories for each general event and each location. This resulted in the constitution of fifteen pairs of past events that were part of a same event cluster but did not happen in the same location, fifteen pairs of past events that happened in the

[1] In the present study, the term 'general event' as used during the pre-scan and scanning sessions referred to events extended in time (or short 'autobiographical periods'; Thomsen, 2015), and not to repeated events (for further discussion of the various types of general events, see e.g. Conway and Pleydell-Pearce, 2000). Indeed, our aim was to collect specific events that are not only part of higher-order clusters, but also that are clearly distinct from each other, which would be difficult to produce on the basis of repeated events.

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same location but are not part of the same event cluster, and fifteen pairs of unrelated past events.

In total, ninety event pairs were thus obtained: fifteen event pairs for each of the six conditions (i.e., future event cluster; future location; future unrelated; past event cluster; past location; past unrelated). The order of presentation of temporal orientation (past versus future) and conditions (event cluster versus location) in the pre-scan interview was counterbalanced across participants.

Scanning session

Stimuli were presented using Cogent 2000 (Wellcome Department of Imaging Neuroscience, University College London, London, UK) software implemented in MATLAB (www.mathworks.com). They were displayed on a screen positioned at the rear of the scanner, and reflected on a mirror located on the head coil in front of the eyes of participants. Before starting the task, participants were shown examples of fictive (but coherent) event pairs to familiarize them with the display, the presentation delay and the response pad. During the scan session, the 90 event pairs were presented in a pseudo-random order to ensure that two event pairs of a same condition were not too far from one another (no more than 7 trials) and did not immediately follow each other.

Each trial began with the display of the time period (i.e., past or future), written in yellow on a black background on the top of the screen and presented during 1 s. Then, the description of the event pair appeared in the center of the screen for 6 s, written in white on a black background. In response to each event pair, participants had to identify the type of relation that links the two specific events. Three possible responses were provided: the two events could be linked because they are part of the same general event (i.e., they share the same theme or goal, and/or are causal linked to each other); the two events could be linked because they occur in the same location; or the two events are unrelated to each other. Participants were asked to press the key corresponding to their answer on a pad (i.e. 1 for the same general event; 2 for the same location; 3 for no relation) and to continue to think about the two events and about how they are related to each other (i.e., to the shared theme or common location) during the rest of the display. When there was no relation between the two specific events, participants were only asked to think about these events. Between each trial, a fixation cross was presented with a duration jittered between 2 and 6 s. The whole task lasted approximately 20 min.

fMRI data acquisition

fMRI time series were acquired on a 3 T head-only scanner (Magnetom Allegra, Siemens Medical Solutions, Erlangen, Germany) operated with the standard transmit–receive quadrature head coil. Multislice T2*-weighted functional images were acquired with a gradient-echo EPI sequence using axial slice orientation and covering the whole brain (34 slices, field of view [FoV] = 192×192 mm^2, voxel size $3 \times 3 \times 3$ mm^3, 25% interslice gap, matrix size $64 \times 64 \times 34$, repetition time [TR] = 2040 msec, echo time [TE] = 30 msec, flip angle = 90°). On average, 500 functional volumes were acquired per participants (SD = 3.50; range: 492-504) and the three first volumes were discarded to avoid T1 saturation effects. After the EPI acquisition, a gradient-recalled sequence was applied to acquire two complex images with different TEs (TE = 4.92 and 7.38 msec, respectively; TR = 367 msec, FoV = 230×230 mm^2, 64×64 matrix, 34 transverse slices with 3 mm thickness and 25% interslice gap, flip angle = 90°, bandwidth = 260 Hz/pixel) and generate field maps for distortion correction of the EPI images. A structural MRI scan was obtained at the end of the session (T1-weighted 3-D MP-RAGE sequence, TR = 1960 msec, TE = 4.4 msec, FoV = 230×173 mm^2, matrix size $256 \times 192 \times 176$, voxel size $0.9 \times 0.9 \times 0.9$ mm^3).

fMRI data analysis

Data preprocessing

Data were preprocessed using the SPM 8 software (Wellcome Department of Imaging Neuroscience, http//www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB R2010a. EPI time series were corrected for motion and distortion using Realign and Unwarp (Andersson et al., 2001) together with the Fieldmap Toolbox (Hutton et al., 2002). The mean realigned EPI image was coregistered to the structural T1 image, and the coregistration parameters were applied to the realigned EPI time series. The T1 image was segmented into gray matter, white matter, and cerebrospinal fluid, using the unified segmentation approach (Ashburner and Friston, 2005), and the coregistered functional images were normalized to MNI space (voxel size: $2 \times 2 \times 2$ mm^3) using the normalization parameters obtained from the segmentation procedure. Finally, the functional images were smoothed with a Gaussian kernel with FWHM of 8 mm.

Partial least squares analyses

Task-related brain activation was investigated using the PLS Software (http://www.rotman-baycrest.on.ca/pls). PLS uses a multivariate approach (McIntosh et al., 1996; McIntosh and Lobaugh, 2004) that detects whole brain patterns of activity (BOLD signal) related to the experimental design (i.e., tasks). This analysis technique has been widely used in previous neuroimaging studies of autobiographical memory and future-oriented thinking (e.g., Addis et al., 2004a, 2009, 2012; Burianova and Grady, 2007; Burianova et al., 2010; Spreng and Grady, 2010; Gerlach et al., 2014; Robin et al., 2014).

When applied on blocked data, PLS identifies spatial patterns of whole brain activity in the form of orthogonal latent variables (LVs) – based on the covariance matrix of the mean BOLD signal for each block, and a matrix of vectors coding for the design (i.e., the experimental conditions) – that optimally explain the differences between the tasks (Gerlach et al., 2014; Spreng et al., 2010; McIntosh et al., 1996). In other words, each LV emerging from the analysis defines a pattern distributed across the whole brain, and contrasts the experimental conditions depending on their relation (positive or negative) with this pattern. The significance of LVs is determined via permutations tests, and the reliability of the salience (i.e., weight) of brain voxels characterizing latent variables is assessed by a bootstrap estimation of the standard error (BSR) (Efron and Tibshirani, 1986). The salience of each brain voxel is proportional to its contribution to the pattern of covariation identified by the LV, and can have positive or negative values depending on the positive or negative relation existing between this voxel and the repartition of conditions characterizing the LV. There is no need to correct for multiple comparisons in PLS because the salience for each voxel is calculated in one analytic step, contrary to univariate analyses which examine the activation of single voxels independently (Addis et al., 2004a, 2009; Gerlach et al., 2014; McIntosh et al., 1996). In the present study, blocks were defined with a duration of 6 s corresponding to the trial duration (onset = display of the event pair). Only correct responses were included in the analyses, resulting in a mean of 13.87 trials (SD = 1.01) for the past cluster condition, 13.78 trials (SD = 1.31) for the future cluster condition, 14.17 trials (SD = 1.23) for the past location condition, 13.74 trials (SD = 1.21) for the future location condition, 14.70 trials (SD = 0.56) for the past unrelated condition, and 14.65 trials (SD = 0.65) for the future unrelated condition.

Mean-centered PLS analysis. We first conducted a mean-centered PLS analysis (e.g., Addis et al., 2004a, 2009), a data-driven approach in which no a priori contrast is specified. This analysis identifies a set of LVs that best explain the covariation between the dataset and the experimental design. Each LV accounts for a certain portion of the covariance (i.e., between the BOLD signal and the experimental conditions) expressed by its singular value (Addis et al., 2009; McIntosh et al., 1996). In the present study, the statistical significance of each LV was

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calculated using a permutation test with 800 permutations, and the salience of brain voxels characterizing the LVs was assessed using 200 bootstraps. We considered voxels as reliable if they survived to a threshold of ± 3.0, corresponding to $p = .0027$ – consistently with thresholds used in previous studies of autobiographical memory and future thinking that used PLS analyses (e.g., Addis et al, 2009, 2012; Sheldon and Levine, 2013; Robin et al., 2014) – with a cluster size of minimum 20 voxels and a gap of minimum 10 voxels between two peaks. Each condition was considered as contributing reliably to the overall pattern if its confidence interval (CI) did not cross 0, and two conditions were considered as significantly different from each other if their CIs did not cross each other. Each BSR was computed with a 95% CI.

Seed PLS analyses. We also sought to investigate the functional connectivity of regions hypothesized to support the processing of event clusters. More specifically, we hypothesized that the medial and rostrolateral prefrontal cortex would be functionally coupled to posterior cortical regions supporting semantic processing (i.e., lateral temporal and inferior parietal regions) during the processing of event clusters. This hypothesis was tested using seed PLS analyses (McIntosh, 1999). Seed PLS assesses the covariation between activity in one (or a few) region(s) of interest and the rest of the brain, and determines how this covariation varies across tasks (see e.g., Spreng et al., 2010; Spreng and Grady, 2010; McClelland et al., 2014; Gerlach et al., 2014; Addis et al., 2004a; Robin et al., 2014). In the present study, two seeds were selected, which corresponded to the main regions of the mPFC and rostrolateral PFC that were associated with the processing of event clusters in our previous mean-centered PLS analysis (see Results, subsection 3.2.1). The BOLD signal from each seed was extracted using the multiple voxel extraction tool, centered on the peak coordinates (mPFC: x, y, z = 2, 44, 16; rostrolateral PFC: x, y, z = −22, 54, 16) and averaging signal intensity across the three nearest neighboring voxels. These signal intensity values were entered in two separate non-rotated seed PLS analyses, which investigated whether the functional connectivity of each seed with the rest of the brain differs between the event clusters conditions and the other control conditions. For each seed PLS analysis, permutations test and bootstraps estimations of the standard errors were performed as described above with 800 permutations tests, and 200 BSR computed with a 95% CI. As for the previous mean-centered PLS analysis, we considered voxels as reliable if they survived a threshold of ± 3.0 ($p = .0027$), with a cluster size of minimum 20 voxels and a gap of minimum 10 voxels between peaks.

Results

Behavioral results

A 2 (temporal orientation) by 3 (type of relation) repeated measures analysis of variance (ANOVA) conducted on correct responses yielded a significant effect of the type of relation, $F(2, 44) = 9.70$, $p < .001$; $\eta_p^2 = 0.31$. Linear contrasts showed no significant difference between proportions of correct responses for general events ($M = .92$, $SE = .01$) and common locations ($M = .93$, $SE = .01$), $F(1,22) = 0.27$, $p = .61$, but performance in these two conditions was lower than for unrelated pairs ($M = .98$, $SE = .01$), $F(1,22) = 28.60$, $p < .001$ and $F(1,22) = 12.45$, $p = .002$, respectively. There was no main effect of temporal orientation, $F(1, 22) = 1.37$, $p = .25$, $\eta_p^2 = 0.06$, and no interaction between the type of relation and temporal orientation, $F(2, 44) = 0.69$, $p = .51$, $\eta_p^2 = 0.03$.

A 2 (temporal orientation) by 3 (type of relation) repeated measures ANOVA conducted on response times (RTs) also yielded a significant effect of the type of relation linking specific events, $F(2, 44) = 32.32$, $p < .001$, $\eta_p^2 = 0.60$. Linear contrasts showed that RTs were faster for unrelated pairs ($M = 2896$ ms, $SE = 115$ ms) than for both general events ($M = 3485$ ms, $SE = 93$ ms), $F(1, 22) = 48.35$, $p < .001$, and common

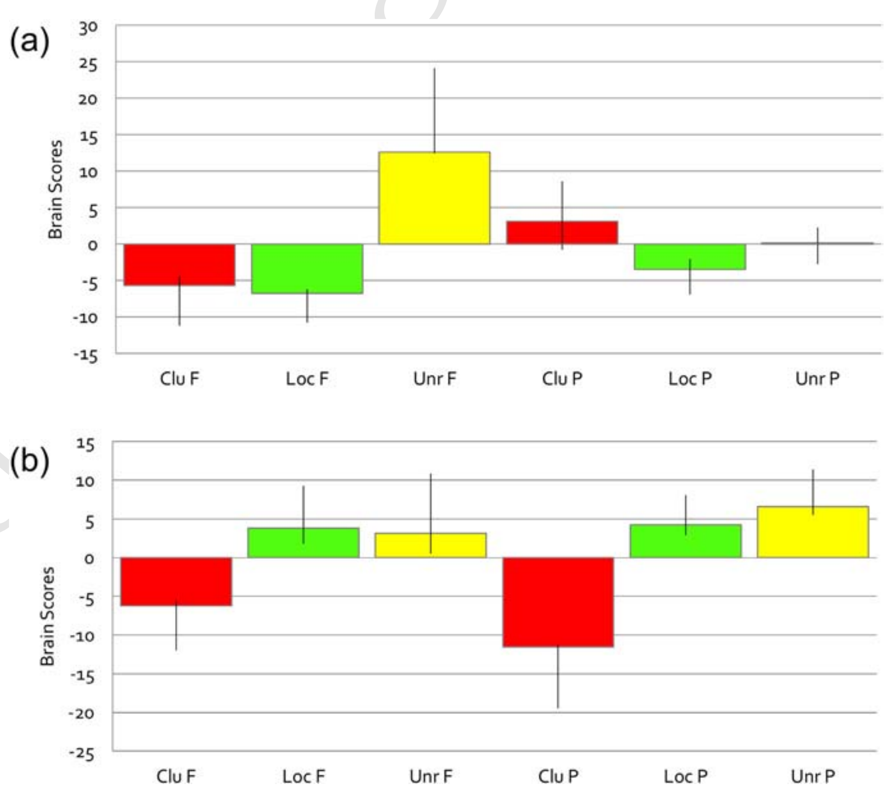

Fig. 1. Mean brain scores per condition for LV1 and LV2 in the mean-centered PLS analysis. (a) LV 1 explains 27.28% of the cross-block covariance (singular value = 16.08; $p = .03$) and (b) LV 2 explains 27.21% of the cross-block covariance (singular value = 16.06; $p = .03$). Error bars represent the 95% bootstrapped confidence intervals. Clu F = future cluster; Loc F = future location; Unr F = future unrelated; Clu P = past cluster; Loc P = past location; Unr P = past unrelated.

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Table 1
Brain regions associated with LV1 in the mean-centered PLS analysis.

Region	MNI coordinates			BSR	Cluster size
	x	y	z		
Future unrelated > future related					
L inferior frontal sulcus	−34	22	28	4.30	34
R middle frontal gyrus	40	52	12	3.99	52
R supplementary motor cortex	14	4	66	4.62	34
L precentral sulcus	−56	10	28	4.31	32
R precentral sulcus	46	12	44	3.62	20
L postcentral gyrus	−54	−12	36	5.37	77
L postcentral sulcus	−44	−24	36	4.76	68
R inferior temporal gyrus	34	0	−40	3.90	46
R supramarginal gyrus	42	−46	30	4.56	47
L supramarginal gyrus	−62	−50	34	3.72	49
L hippocampus	−34	−24	−16	3.92	27
L thalamus	−18	−18	18	4.76	38
L caudate	−18	10	12	4.60	24
R precuneus	8	−50	38	4.52	196
R cuneus	8	−70	14	4.20	73
L lingual gyrus	−22	−70	−4	5.76	60
L middle occipital gyrus	−28	−66	28	4.02	52
Future related > future unrelated					
L orbitofrontal cortex	−20	38	−12	−4.01	22
B subgenual cingulate cortex	0	30	−6	−3.86	23
L Cerebellum	−16	−42	−42	−4.25	23

Note: threshold = ±3 (p = .0027) and minimum cluster size = 20 voxels. B: bilateral; R: right; L: left.

Table 2
Brain regions associated with LV2 in the mean-centered PLS analysis.

Region	MNI coordinates			BSR	Cluster size
	x	y	z		
Cluster > controls					
L rostrolateral prefrontal cortex	−22	54	16	−3.95	29
B medial prefrontal cortex	2	44	16	−4.73	91
L medial prefrontal cortex	−6	54	16	−3.87	31
R anterior cingulate cortex	10	36	24	−4.18	46
L temporal pole	−32	10	−22	−4.61	38
L inferior temporal gyrus	−50	−60	−8	−3.77	21
L middle temporal gyrus	−48	−48	2	−4.37	28
L supramarginal/angular gyrus	−44	−46	24	−5.63	192
R frontoparietal operculum	48	−10	16	−4.44	127
R insula	38	26	6	−4.28	34
L insula	−40	2	−16	−4.09	35
R thalamus	20	−18	−2	−3.81	25
L globus pallidus	−12	0	−4	−4.31	54
L caudate	−6	12	12	−3.85	35
R caudate	18	28	2	−3.45	36
L putamen	−24	−10	10	−3.56	27
L parahippocampal gyrus	−22	−38	−10	−3.85	49
B retrosplenial cortex	6	−46	2	−4.62	184
L fusiform gyrus	−24	−36	−20	−3.67	38
R cuneus/lingual gyrus	8	−78	20	−4.94	356
L lingual gyrus	−16	−76	−8	−4.26	93
R cerebellum	12	−72	−48	−4.30	21
R cerebellum	40	−66	−42	−4.22	37
L cerebellum	−6	−66	−28	−3.75	30
Controls > cluster					
L orbitofrontal cortex	−42	36	−10	4.10	25
R superior frontal gyrus	14	14	52	6.47	73
R superior frontal gyrus	18	−2	50	5.18	214
R supramarginal gyrus	62	−36	40	5.10	104
R intraparietal sulcus	38	−36	50	4.73	71
R thalamus	18	−18	12	5.49	56
R precuneus	10	−62	60	4.45	36

Note: threshold = ±3 (p = .0027) and minimum cluster size = 20 voxels. B: bilateral; R: right; L: left.

location (M = 3343 ms, SE = 95 ms), $F(1, 22) = 24.90$, $p < .001$, and faster for common locations than for general events, $F(1, 22) = 8.61$, $p = .008$. There was no main effect of temporal orientation, $F(1, 22) = 0.810$, $p = .0.38$, $\eta_p^2 = 0.04$, and no interaction between the type of relation and temporal orientation, $F(2, 44) = 1.14$, $p = .33$, $\eta_p^2 = 0.05$.

fMRI results

Mean-centered PLS analysis

The mean-centered PLS analysis identified two significant latent variables which accounted for a similar proportion of the covariance in the data. The first LV (LV1: p = .03, singular value = 16.08) accounted for 27.28% of the cross-block covariance. The interpretation of this first LV is not straightforward, but it appeared to mainly distinguish the future unrelated condition from the future cluster and location conditions (see Fig.1a). Brain regions showing increased activity for unrelated future events included the bilateral lateral prefrontal cortex, premotor and somatosensory cortices, inferior parietal cortex, right inferior temporal gyrus, left hippocampus, precuneus, and occipital areas (see Table 1 and Fig. S1). Regions that were more associated with the future cluster and location conditions relative to the future unrelated condition included left prefrontal areas (orbitofrontal cortex and middle frontal gyrus), the subgenual cingulate cortex, and cerebellum (see Table 1 and Fig. S1).

The second latent variable (LV2: p = .03, singular value = 16.06) accounted for 27.21% of the cross-block covariance and revealed distinct patterns of brain activity for conditions involving past and future event clusters relative to all the other conditions. The brain scores indicated that all six conditions significantly contributed to the overall pattern (see Fig. 1b). The pattern of brain activity associated with event clusters versus the four control conditions are described in Table 2 and shown on Fig. 2. In line with our predictions, thinking about past and future events that were part the same event cluster was associated with increased activity in a set of frontal, temporal, and parietal regions. More specifically, the processing of event clusters was associated with activity in the bilateral medial and left rostrolateral prefrontal cortex (i.e., medial and lateral parts of Brodmann's area 10), left lateral temporal cortex (i.e., middle/inferior temporal gyrus and temporal pole), and left inferior parietal cortex (i.e., supramarginal gyrus extending to the angular gyrus). Increased activity was also detected in a number of other (non-predicted) regions, including the retrosplenial cortex, left parahippocampal gyrus, left fusiform gyrus, left lingual gyrus, right cuneus (extending to the lingual gyrus), bilateral insula, anterior cingulate cortex, thalamus, striatum, and cerebellum.

Compared to the processing of event clusters, the four control conditions (events occurring in a same location and unrelated events) were associated with a different pattern of brain activity, including the left orbitofrontal cortex, right superior frontal gyrus, right parietal regions (precuneus, intraparietal sulcus, and supramarginal gyrus), and thalamus (see Table 2 and Fig. S2).[2]

Seed PLS analyses

We also sought to investigate the distributed patterns of functional connectivity associated with the medial and rostrolateral prefrontal regions identified as being related to the processing of event clusters in the above analysis. The BOLD signal from the two main prefrontal regions that were associated with the processing of event clusters in the mean-centered PLS analysis were entered in two non-rotated seed PLS analyses, which investigated whether the functional connectivity of each of these regions with the rest of the brain differed between the cluster conditions and the other conditions.

The analysis with the medial prefrontal seed did not reveal a reliable pattern of functional connectivity when past and future events were collapsed together in the specified contrast (Event clusters > Location/

[2] We also performed a non-rotated PLS analysis in which the contrast between event clusters and the other conditions was specified a priori. The results of this additional analysis were consistent with the mean-centered analysis.

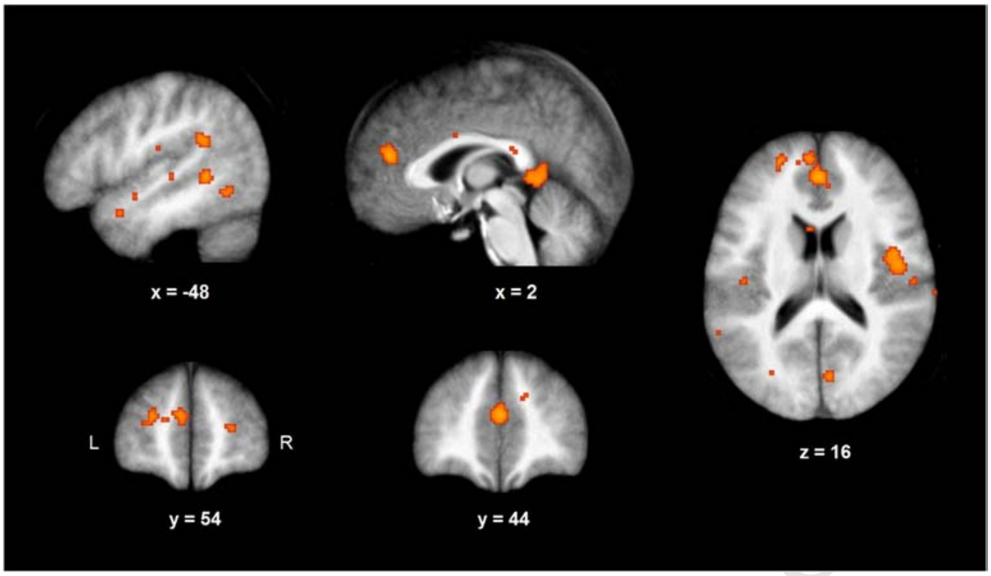

Fig. 2. Brain regions showing higher activity for event clusters relative to control tasks. Threshold of the BSR = −3 ($p = .0027$). Activations are displayed on the mean structural MRI of participants. Coordinates are reported in MNI space.

Table 3
Brain regions showing functional connectivity with the medial prefrontal cortex seed when processing past event clusters.

Region	MNI coordinates			BSR	Cluster size
	x	y	z		
R rostrolateral prefrontal cortex	36	54	−2	4.06	52
L rostrolateral prefrontal cortex	−28	58	−6	4.30	80
B ventromedial prefrontal cortex	2	30	−14	5.24	135
R medial prefrontal cortex	14	54	10	5.30	30
L medial prefrontal/anterior cingulate cortex	−6	44	0	5.65	276
B dorsomedial prefrontal cortex	−4	30	56	4.25	100
B anterior cingulate cortex	4	26	16	5.67	103
R inferior frontal gyrus	56	24	16	4.70	54
R inferior frontal gyrus	52	24	−4	4.81	159
R inferior frontal gyrus	48	12	30	6.21	76
L inferior frontal gyrus	−50	28	8	5.53	320
L middle frontal gyrus	−36	14	46	5.04	36
L superior frontal gyrus	−16	18	68	4.17	42
B cingulate gyrus	−2	−2	34	4.44	118
L. precentral gyrus	−26	−22	62	5.07	108
L precentral gyrus	−12	−26	76	5.26	71
R postcentral gyrus	66	−12	18	4.06	21
L postcentral gyrus	−20	−38	58	3.93	60
L middle temporal gyrus	−54	2	−18	8.74	161
L middle temporal gyrus	−48	−20	−12	4.86	41
L middle temporal gyrus	−60	−60	8	4.51	27
R superior temporal sulcus	46	−30	−4	3.90	21
L superior temporal gyrus	−64	−52	22	5.63	114
R superior temporal gyrus	62	−8	−2	3.72	20
L superior temporal gyrus	−48	−4	−2	3.87	30
R frontoparietal operculum	38	−24	22	5.48	90
R frontoparietal operculum/insula	48	4	12	4.39	75
R angular gyrus	46	−66	28	4.81	40
L thalamus	−8	−22	18	3.69	41
R caudate	12	12	0	6.32	77
L fusiform/parahippocampal gyrus	−28	−28	−22	4.39	24
L lingual/parahippocampal/fusiform gyrus	−18	−44	−4	5.12	232
L posterior cingulate/retrosplenial cortex	−8	−56	14	5.17	22
R calcarine sulcus	2	−94	8	4.80	40
L cuneus	−6	−86	20	4.48	32
R cuneus	18	−58	22	3.54	23
L cerebellum	−50	−56	−36	4.07	20
B cerebellum	0	−44	−10	3.68	26

Note: threshold = 3 ($p = .0027$) and minimum cluster size = 20 voxels. B: bilateral; R: right; L: left.

Unrelated; $p = .245$). We then conducted additional analyses by contrasting event clusters with the location and unrelated conditions, separately for past and future events. This showed that the functional connectivity of the mPFC was significantly modulated by the processing of event clusters for past events ($p = .036$), but not for future events ($p = .155$). When processing past event clusters, the mPFC showed increased functional coupling with a network including medial and lateral prefrontal regions bilaterally, the lateral temporal cortex bilaterally, the left posterior cingulate/retrosplenial cortex and fusiform/parahippocampal gyri, and the occipital cortex (see Table 3 and Fig. 3). Activity in this network strongly correlated with activity in the mPFC seed during the processing of past event clusters ($r = .88$), but not in the past location ($r = .01$) and past unrelated ($r = .14$) conditions.

The analysis with the rostrolateral prefrontal seed revealed that the functional connectivity of this region was significantly modulated during the processing of past and future event clusters ($p = .004$). More specifically, the rostrolateral PFC showed increased functional coupling with a network including lateral prefrontal regions bilaterally, the lateral temporal cortex bilaterally, left hippocampus, retrosplenial cortex, inferior parietal cortex bilaterally, precuneus, and occipital cortex (see Table 4 and Fig. 4). Activity in this network strongly correlated with activity in the rostrolateral PFC seed during the processing of both past ($r = .82$) and future ($r = .72$) event clusters, but not in the location ($r = -.04$ and $r = -.001$, for past and future events, respectively) and unrelated ($r = -.05$ and $r = -.003$, for past and future events, respectively) conditions.

Discussion

The present study aimed to investigate the neural bases of the autobiographical framework used to organize sets of specific events in coherent themes and causal sequences—referred to as event clusters—when remembering the past and envisioning the future. As predicted, increased activity was found in a set of brain regions supporting conceptual and integrative processing (i.e., mPFC, rostrolateral PFC, lateral temporal, and inferior parietal cortices) when participants considered pairs of events that were thematically and/or causally related to each other (i.e., events embedded in the same event cluster), compared to events that only shared a surface feature (i.e., their location) or that were unrelated to each other. Importantly, these regions were not only

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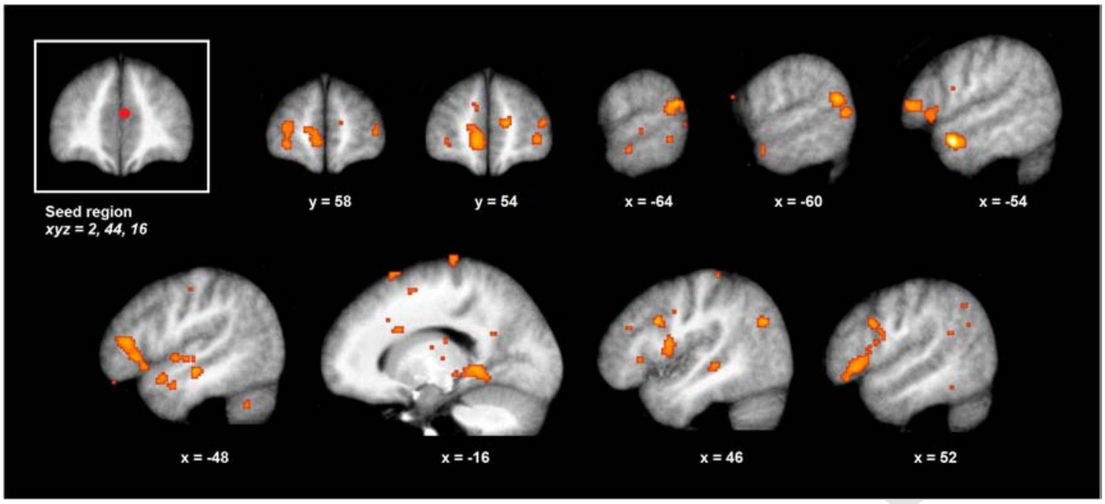

Fig. 3. Brain regions showing functional connectivity with the mPFC seed when processing past event clusters. Threshold of the BSR = 3 (p = .0027). Activations are displayed on the mean structural MRI of participants. Coordinates are reported in MNI space.

recruited for clusters of past events, but also for clusters of envisioned future events. Functional connectivity analyses further revealed that prefrontal regions (mPFC and rostrolateral PFC) showed increased coupling with more posterior regions (temporal, parietal, and occipital cortices) when processing event clusters. Overall, these findings suggest that largely similar mechanisms are involved in organizing events in thematic clusters when remembering the past and imagining the future.

In line with our prediction, the processing of past and future events that were members of the same cluster was associated with increased activity in the medial part of the prefrontal cortex. The mPFC is one of the most commonly activated regions in studies of autobiographical remembering and prospective thinking (for meta-analyses, see Benoit and Schacter, 2015; Kim, 2012; Martinelli et al., 2013; McDermott et al., 2009; Spreng et al., 2009; Stawarczyk and D'Argembeau, 2015; Svoboda et al., 2006), but its exact function is not yet fully understood. This region is not only activated when representing specific past and future events, but also when processing more abstract self-related information, such as traits (van der Meer et al., 2010), goals (Stawarczyk and D'Argembeau, 2015), and knowledge of personal facts and general events (Martinelli et al., 2013). In addition, the mPFC is involved in creating abstract knowledge derived from regularities across multiple episodic experiences, and in relating and integrating incoming information to these existing knowledge structures (Brod et al., 2013; Kroes and Fernandez, 2012; Preston and Eichenbaum, 2013; van Kesteren et al., 2012), an integrative process that may notably contribute to determining the personal/affective value of stimuli and mental contents (Benoit et al., 2014; D'Argembeau, 2013; Roy et al., 2012). On the basis of these previous studies and the present finding that the mPFC is more activated when processing events that are part of the same cluster, we suggest that an important function of the mPFC in autobiographical remembering and future thinking might be to link and integrate specific event representations to higher-order conceptual autobiographical knowledge (e.g., to personal goals and general knowledge about the events and periods that constitute a person's life). Through this integrative process, the mPFC might contribute to contextualize specific event representations within one's life story, thus rendering memories and future thoughts truly autobiographical (Conway, 2005; D'Argembeau, 2015; Fivush, 2011; Habermas and Bluck, 2000).

Besides the mPFC, the pattern of activations associated with the processing of event clusters also included the left rostrolateral PFC. This region is thought to support the most complex aspects of cognitive control (Koechlin and Hyafil, 2007; Ramnani and Owen, 2004) and, in particular, to enable the joint consideration, comparison, and integration of several mental representations or relations (Christoff et al., 2001; Wendelken et al., 2011). The activation of the rostrolateral PFC in the present study might reflect the operation of such controlled processes in determining or evaluating the relational dimensions that link events in higher-order clusters. In particular, causal relations are one of the key relational dimensions that characterize event clusters, for both past and future events (Brown and Schopflocher, 1998; D'Argembeau and Demblon, 2012; Demblon and D'Argembeau, 2014), and the rostrolateral PFC might contribute to making these causal connections between represented events (Barbey and Patterson, 2011).

While the medial and rostrolateral PFC might contribute to linking specific events together and integrating them with higher-order autobiographical knowledge, such knowledge is likely not stored in the prefrontal cortex, but rather in more posterior regions that support the representation of semantic information. Indeed, we found that processing events that were part of the same event cluster engaged regions of the left temporal and parietal cortices that have been previously associated with semantic representations (Binder and Desai, 2011; Binder et al., 2009; Jefferies, 2013). The lateral temporal cortex might store abstract autobiographical knowledge (e.g., general personal information, knowledge about the facts and events of one's life, and personal goals; Renoult et al., 2012; Stawarczyk and D'Argembeau, 2015; Svoboda et al., 2006) that is used for linking and organizing events in clusters. The exact function of the inferior parietal cortex remains debated, but it might contribute to the control (Jefferies, 2013) or integration (Binder et al., 2009) of semantic information, or might indicate an attentional capture by retrieved knowledge (Cabeza et al., 2012).

Functional connectivity analyses further showed that these prefrontal and more posterior regions were coupled together during the processing of event clusters. More specifically, the rostrolateral PFC was functionally connected to regions that have been associated with the controlled activation/selection and representation of semantic information (inferior frontal gyrus, lateral temporal cortex, inferior parietal cortex; Binder et al., 2009; Jefferies, 2013), as well as regions that might represent episodic details of specific events (hippocampus, retrosplenial cortex, precuneus, and visual cortex; Addis et al., 2004b; Daselaar et al., 2008; Martinelli et al., 2013). This functional coupling is consistent with the view that the rostrolateral PFC might support the joint consideration and integration of multiple sources of information to determine the relational dimensions that link events in clusters.

The mPFC also showed increased functional connectivity with regions supporting semantic and episodic representations when processing event clusters but, interestingly, this coupling was only significant for past events. As discussed above, the mPFC is thought to play a role in evaluating and integrating incoming information with prior

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Table 4
Brain regions showing functional connectivity with the left rostrolateral prefrontal cortex seed when processing past and future event clusters.

Region	MNI coordinates			BSR	Cluster size
	x	y	z		
L orbitofrontal cortex	−24	28	−8	5.29	41
L rostrolateral prefrontal cortex	−14	60	2	5.24	41
L rostrolateral prefrontal cortex	−26	50	−2	4.10	35
R rostrolateral prefrontal cortex	28	54	12	4.44	32
L inferior frontal gyrus	−58	16	26	5.99	562
L inferior frontal gyrus	−48	20	−2	4.42	179
R inferior frontal gyrus	60	26	12	4.57	54
R inferior frontal gyrus	46	12	30	4.50	30
L middle/superior frontal gyrus	−22	24	48	4.42	143
L middle frontal gyrus	−42	12	48	4.90	133
B dorsomedial prefrontal cortex	0	32	56	4.96	41
R anterior cingulate cortex	12	28	34	4.81	29
L anterior cingulate cortex	−10	12	40	3.94	26
B anterior cingulate cortex	0	16	26	5.51	48
R cingulate cortex	12	−2	40	3.74	23
R precentral sulcus	44	6	16	4.35	28
L precentral gyrus/frontoparietal operculum	−48	−2	18	5.82	130
L precentral gyrus	−32	−16	62	4.95	58
R precentral gyrus	20	−20	58	4.81	26
L paracentral lobule	−6	−38	68	6.76	132
L postcentral gyrus	−38	−28	46	5.30	104
R inferior temporal gyrus	46	−50	−10	4.77	43
L inferior/middle temporal gyrus	−56	−20	−24	4.82	77
L inferior temporal gyrus	−44	−66	−8	4.62	57
L middle temporal gyrus	−64	−46	−4	4.22	48
R superior temporal sulcus	48	−22	−10	4.69	85
L supramarginal gyrus	−40	−50	44	4.33	165
L supramarginal gyrus	−50	−32	46	5.66	98
R angular gyrus	54	−58	28	4.02	56
L hippocampus	−26	−28	−8	4.21	31
L amygdala	−26	2	−16	5.00	30
B retrosplenial cortex	−10	−46	0	4.85	308
L precuneus	−8	−74	36	4.65	116
L precuneus	−8	−58	28	4.48	99
L cuneus	−6	−86	22	4.51	30
R lingual gyrus	8	−68	−10	4.45	38
L calcarine sulcus	−4	−98	−6	5.00	148
L fusiform/inferior occipital gyrus	−26	−72	−12	5.01	118
R fusiform/inferior occipital gyrus	42	−74	−14	5.35	192
R inferior occipital gyrus	28	−94	−12	3.99	48
L middle/superior occipital gyrus	−22	−82	22	4.60	38
L middle/inferior occipital gyrus	−34	−96	−4	4.41	111
R cerebellum	26	−82	−30	6.47	559
R cerebellum	36	−40	−32	5.57	51
R cerebellum	8	−78	−38	4.35	49
L cerebellum	−26	−70	−24	4.96	389

Note: threshold = 3 ($p = .0027$) and minimum cluster size = 20 voxels. B: bilateral; R: right; L: left.

knowledge, which is itself stored in more posterior regions (Brod et al., 2013; Kroes and Fernandez, 2012; Preston and Eichenbaum, 2013; van Kesteren et al., 2012). The present finding that the functional connectivity of the mPFC with posterior regions increased only for past events might indicate differences between the past and future in terms of the amount of information supporting event clusters. For example, although people possess general autobiographical knowledge both about their past and their anticipated future (e.g., Anderson and Dewhurst, 2009; D'Argembeau and Mathy, 2011), such knowledge may be less elaborated for the future than the past due to the inherent uncertainty associated with prospective thought (see Suddendorf, 2010, for further discussion of differences between remembering and future thinking). The level of functional connectivity of the mPFC might thus reflect the amount of autobiographical knowledge available for integrating events in clusters. In a related vein, lesion and neuroimaging studies have shown that the mPFC is involved in processing self-related traits (e.g., Philippi et al., 2012; van der Meer et al., 2010) and our functional connectivity results might thus indicate that past event clusters provided more information about an individual's traits than future event clusters. These hypotheses could be tested in future studies by assessing to what extent general autobiographical information and other self-related knowledge (such as traits) is accessed when thinking about past and future event clusters.

The finding that the cluster condition was associated with higher activity in retrosplenial, parahippocampal, and occipital cortices relative to the location condition was somewhat unexpected. These regions are commonly involved in studies of autobiographical remembering and future thinking (see e.g., Benoit and Schacter, 2015; Kim, 2012; Martinelli et al., 2013; McDermott et al., 2009; Stawarczyk and D'Argembeau, 2015), and their activity has been found to increase with the amount of contextual information retrieved for constructing event representations (Szpunar et al., 2009; Gilmore et al., 2014). Retrosplenial and parahippocampal cortices have been shown to play an important role in spatial processing (Epstein, 2008; Miller et al., 2014; Vann et al., 2009), and the representation of a coherent spatial context is indeed a key component of specific past and future thoughts (Hassabis and Maguire, 2007). Therefore, one could have expected that, in the present study, retrosplenial, parahippocampal, and occipital cortices would have been more activated when processing events that shared the same location rather than events that were part of the same cluster, as visuo-spatial information was likely processed at a deeper level in the former condition. However, the retrosplenial and parahippocampal cortex could play a broader role in generating various types of associations (Bar et al., 2007). Perhaps events that were part of clusters tended to automatically elicit more associations (e.g., additional events that were also part of the same cluster) than unclustered events, and the increased activations observed here might in part reflect such associative processes. This explanation is clearly tentative and additional studies will be required to further investigate this possibility.

The mean-centered PLS analysis also revealed a latent variable that seemed to mainly differentiate between pairs of related versus unrelated future events. The neural pattern associated with the future unrelated condition included lateral frontal, sensorimotor, and occipital regions, as well as the left hippocampus. The interpretation of this result is not straightforward but the observed network could indicate an increased representation of episodic details when participants imagined unrelated future events. Indeed, participants were instructed to think about individual events in case they did not detect any relation between them, which might have favored the representation of event specific details to a greater extent than conditions in which participants also had to focus on higher-order relations among events. This possibility could be investigated in future studies by assessing the kinds of information (e.g., episodic, semantic, and autobiographical) that are activated when considering related versus unrelated future events.

Finally, it is worth mentioning that future events were not generated for the first time during the scanning session, but had already been thought about during the pre-scan interview and perhaps on other previous occasions; recent findings indeed suggest that many episodic future thoughts do not refer to newly imagined events, but instead represent "memories of the future" (Jeunehomme and D'Argembeau, in press; Szpunar et al., 2013). The present findings might thus be restricted to future event representations that have already been integrated with higher-order autobiographical knowledge, and it would be interesting in future studies to investigate how newly imagined events are initially linked to other anticipated events and pre-existing autobiographical knowledge (and perhaps in turn modify and adapt these prior representations).

To conclude, the present findings provide evidence that a set of brain regions within the core network involved in autobiographical remembering and future thinking support the integration of single events in a meaningful autobiographical framework. The medial PFC might play a pivotal role in mediating the integration of specific events with conceptual autobiographical knowledge 'stored' in more posterior regions, and the rostrolateral PFC might support controlled processes involved

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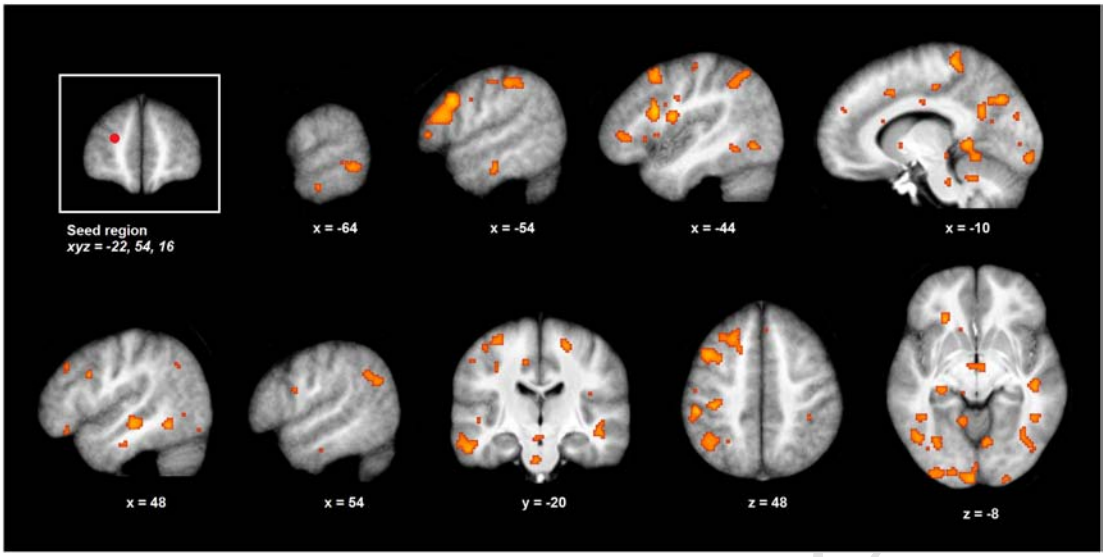

Fig. 4. Brain regions showing functional connectivity with the rlPFC seed when processing past and future event clusters. Threshold of the BSR = 3 ($p = .0027$). Activations are displayed on the mean structural MRI of participants. Coordinates are reported in MNI space.

in this relational integration. Through this integrative process, this set of brain regions might contribute to the attribution of an overarching meaning to representations of specific past and future events, by contextualizing them with respect to personal goals and general knowledge about one's life.

Uncited reference

Humphreys and Lambon Ralph, 2014

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.11.062.

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