

Two critical brain networks for generation and combination of remote associations

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Recent functional imaging findings in humans indicate that creativity relies on spontaneous and controlled processes, possibly supported by the default mode and the fronto-parietal control networks, respectively. Here, we examined the ability to generate and combine remote semantic associations, in relation to creative abilities, in patients with focal frontal lesions. Voxel-based lesion-deficit mapping, disconnection-deficit mapping and network-based lesion-deficit approaches revealed critical prefrontal nodes and connections for distinct mechanisms related to creative cognition. Damage to the right medial prefrontal region, or its potential disrupting effect on the default mode network, affected the ability to generate remote ideas, likely by altering the organization of semantic associations. Damage to the left rostrolateral prefrontal region and its connections, or its potential disrupting effect on the left fronto-parietal control network, spared the ability to generate remote ideas but impaired the ability to appropriately combine remote ideas. Hence, the current findings suggest that damage to specific nodes within the default mode and fronto-parietal control networks led to a critical loss of verbal creative abilities by altering distinct cognitive mechanisms.

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Abbreviations: CAT = Combined Associates Task; DMN = default mode network; FGAT = Free Generation of Associates Tasks; FPCN = fronto-parietal control network; rl/rmPFC = rostrolateral/rostromedial prefrontal cortex; VLSM = voxel-based lesion-symptom mapping

Introduction

The concept of creativity is imbued with two contradictory notions. First, unusual and creative ideas emerge from relaxing the constraints and letting the mind wander freely and spontaneously. Second, a creative production is

usually considered to be the result of goal-directed cognition that involves high-level control functions such as mental manipulation, abstract thinking, or planning. This paradox reflects the involvement of both uncontrolled spontaneous associative thinking and controlled effortful thinking in creativity (Gabora, 2010; Mok, 2014). Recent

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psychological studies support this claim, by showing the contribution of controlled processes, including cognitive inhibition, switching, or working memory (Gilhooly *et al.*, 2007; Nijstad *et al.*, 2010; Nusbaum and Silvia, 2011; Benedek *et al.*, 2012a; De Dreu *et al.*, 2012; Lee and Theriault, 2013; Silvia *et al.*, 2013; Edl *et al.*, 2014), as well as the role of spontaneous associative thinking (Merten and Fischer, 1999; Gruszka and Necka, 2002; Faust and Lavidor, 2003; Rossmann and Fink, 2010; Benedek *et al.*, 2012b; Beaty *et al.*, 2014a), in creative abilities. The role of associative thinking abilities in creativity depends on the flexible organization of associations between elements of one's semantic knowledge (Mednick, 1962; Mednick *et al.*, 1964a; Kenett *et al.*, 2014; Kenett and Austerweil, 2016). Hence, creativity, defined as 'the forming of associative elements into new combinations' (Mednick, 1962; Mednick *et al.*, 1964a, b), depends on associative thinking abilities (involving the spontaneous activation of semantic associates) and on the ability to combine these elements according to given constraints (involving controlled processes; Chermahini *et al.*, 2012; Lee and Theriault, 2013; Jones and Estes, 2015). However, little is known regarding the brain mechanisms supporting the associative and controlled processes involved in the generation and the combination of creative ideas in the human brain.

Preliminary evidence from functional imaging (Dietrich and Kanso, 2010; Gonen-Yaacovi *et al.*, 2013; Boccia *et al.*, 2015) and from patient studies (Rankin *et al.*, 2007; de Souza *et al.*, 2010; Shamay-Tsoory *et al.*, 2011; Abraham *et al.*, 2012; Barbey *et al.*, 2013) demonstrated the involvement of prefrontal and posterior parietal regions in creativity, emphasizing the role of the fronto-parietal control-related network (FPCN; Vincent *et al.*, 2008; Smith *et al.*, 2009; Woolgar *et al.*, 2010; Cole *et al.*, 2013; Power and Petersen, 2013; Parlatini *et al.*, 2017) in creative thinking. Other neuroimaging approaches based on interindividual variability in morphometry (Jung *et al.*, 2010b, 2013, 2015; Takeuchi *et al.*, 2010; Zhu *et al.*, 2013; Fink *et al.*, 2014; Kühn *et al.*, 2014; Chen *et al.*, 2015; Jauk *et al.*, 2015) or in functional connectivity (Takeuchi *et al.*, 2012; Beaty *et al.*, 2014a; Chen *et al.*, 2014; Cousijn *et al.*, 2014; Wei *et al.*, 2014), have highlighted the role of the default mode network (DMN) in creative abilities. The DMN may play an important role in creative idea generation since its activity is thought to reflect associative cognition, contributing to internally-generated thoughts, mind wandering, and semantic and episodic memory (Buckner *et al.*, 2008; Binder *et al.*, 2009; Christoff *et al.*, 2009; Andrews-Hanna *et al.*, 2010; Wirth *et al.*, 2011; Fox *et al.*, 2015; Humphreys *et al.*, 2015; Xu *et al.*, 2016). Although DMN activity has been initially described as anti-correlated with FPCN activity and decreased with mental efforts and cognitive control (Raichle, 2015), several recently published articles indicate that the DMN and FPCN networks cooperate during creative performance (Ellamil *et al.*, 2012; Beaty *et al.*, 2014b,

2016; Chen *et al.*, 2014; Pinho *et al.*, 2014). Overall, the integration of psychological and neuroimaging findings indirectly suggests that creativity relies on associative abilities that may be supported by the DMN, combined with cognitive control processes that are supported by control-related networks. The lesion approach may be especially useful in testing this hypothesis and would clarify whether distinct damage to the two functional networks would differently affect the associative and controlled processes involved in the formation of creative ideas.

In this study, we address this new question by examining creative abilities in patients with focal frontal brain lesions with a focus on the associative and controlled processes involved in the generation and combination of remote associations. These processes were explored by using two tasks: (i) a verbal associative combination task (the Combined Associates Task, CAT), adapted from Mednick's task (1962), which allowed us to estimate the ability to form new combinations between remote associates; and (ii) a free generation of remote associates task (FGAT-distant) that consisted of a simple word-to-word generation task reflecting the ability to intentionally produce remote associations (FGAT-distant condition) with the instruction to think creatively (Prabhakaran *et al.*, 2013). In addition, another free word-to-word generation task (FGAT-first) consisted of giving the first word that came to mind with the aim of exploring spontaneous semantic associations in participants, which can reflect associative thinking abilities. Critical areas predicting performances were revealed using a voxel-based lesion mapping method (VLSM: Bates *et al.*, 2003; Kinkingnéhun *et al.*, 2007). Because various regions likely interact for cognitive functions, we also examine the impact of disconnections of white matter tracts on creative abilities using a recent approach (Thiebaut de Schotten *et al.*, 2015). Finally, we explored *a priori* the impact of damage to the DMN and to the left or right FPCN on the tasks. Together, these analyses revealed specific patterns of damage within these systems that differently affected the ability to freely generate and the ability to appropriately combine remote associations.

Materials and methods

Participants

Twenty-nine right-handed patients (French-native speakers; 17 females; mean age 47.5 years, age ranging from 23 to 75 years) who presented with a unique focal frontal lesion at the chronic stage (>3 months) were included in this study (Table 1). The patients were recruited from the departments of neurology or neuroradiology at Pitié-Salpêtrière, Saint-Antoine and Lariboisière hospitals in Paris. Patients with a history of psychiatric or neurological disease, drug or psychotropic abuse, or MRI contraindications were not included. Patients with impaired semantic memory [assessed using short French versions of a naming test and a semantic

Table 1 Demographic and clinical data for the patients included in the study

Patient	Age (years)	Gender	Education (years)	Aetiology	Lesion side	Lesion location
P01	56	F	17	Ischaemic stroke	R	Semioval centre
P03	46	F	17	Ischaemic stroke	L	Posterior MFG
P05	64	M	14	Ischaemic stroke	R	IFG and MFG
P13	67	M	15	Ischaemic stroke	L	Anterior IFG
P19	54	M	22	Ischaemic stroke	R	IFG / MFG white matter
P27	58	M	12	Ischaemic stroke	L	Precentral sulcus
P02	55	M	19	Haemorrhage	L	Rostral PFC / VMPFC
P07	51	M	11	Haemorrhage	B	Rostral PFC
P09	47	M	11	Haemorrhage	R	Cingulate / VMPFC
P10	62	F	13	Haemorrhage	B	Cingulate / VMPFC
P12	46	M	12	Haemorrhage	B	Cingulate / VMPFC
P14	49	M	9	Haemorrhage	B	Cingulate / VMPFC
P16	40	F	22	Haemorrhage	L	Rostral PFC
P17	40	M	14	Haemorrhage	B	Rostral PFC / VMPFC
P20	71	M	17	Haemorrhage	L	Rostral PFC / VMPFC
P25	59	F	16	Haemorrhage	L	VMPFC
P26	26	F	13	Haemorrhage	L	Posterior IFG
P29	75	F	12	Haemorrhage	L	Rostral PFC
P04	50	F	11	Low-grade glioma (excision)	L	Rostral PFC+ / VMPFC
P08	70	F	5	Meningioma (excision)	L	Rostral PFC
P30	52	F	13	Low-grade glioma (excision)	R	MFG
P06	32	F	16	Epilepsy surgery	R	Posterior SFG
P11	41	M	16	Epilepsy surgery	R	IFG / MFG / posterior SFG
P15	36	F	14	Epilepsy surgery	R	Rostral PFC / VMPFC
P18	23	F	16	Epilepsy surgery	R	Rostral PFC
P21	23	F	15	Epilepsy surgery	R	Rostral PFC
P22	27	F	9	Epilepsy surgery	L	Lateral rostral PFC
P23	26	F	13	Epilepsy surgery	L	Precentral gyrus
P24	32	F	14	Epilepsy surgery	L	Posterior medial PFC

Ischaemic strokes affected the middle cerebral artery territory. Haemorrhages were caused by a ruptured aneurism, a spontaneous hematoma, or by a vascular malformation for one patient. Epileptic patients underwent a surgical resection of their epileptic focus, whose origin was cryptogenic, except for two patients who had a dysplasia removed (Patients P21 and P23). Education level corresponds to the number of years since the beginning of school (usually at age 6). The interval is the delay (in months) between the onset of the lesion and testing. B = bilateral; F = female; IFG = inferior frontal gyrus; L = left; M = male; MFG = middle frontal gyrus; R = right; SFG = superior frontal gyrus; vmPFC = ventromedial PFC.

matching test, as described in Merck *et al.* (2011)] or who were not able to understand task instructions were excluded from the study. Descriptive and clinical data are reported in Supplementary Table 1.

The patient performances were compared to those of a group of 54 healthy right-handed, French-native speaker controls (Supplementary Table 2), and who had no history of psychiatric or neurological disease, drug or psychotropic abuse, or MRI contraindication and no cognitive impairment [Mini-Mental State Examination (MMSE) \geq 27/30; Folstein *et al.*, 1975]. Controls were matched to patients for age and years of formal education.

The local ethics committee approved the experiment; all participants provided written informed consent and were paid for their participation.

Neuropsychological testing and control tasks

Neuropsychological tests were administered to all participants, assessing their cognitive status (by MMSE), cognitive and behavioural executive functions (by the Frontal Assessment Battery; Dubois *et al.*, 2000). In addition, participants

performed the Stroop test (Stroop, 1935), a phonemic and a category fluency task, and short French versions of a naming test and a semantic matching test as described in Merck *et al.* (2011), to control for some executive and semantic processes that play roles in the experimental tasks. The Stroop test assesses the ability to inhibit a prepotent response. The performance of fluency tasks depends on a complex set of cognitive processes, including self-initiation of action, semantic retrieval, switching between categories of responses, inhibition, updating and monitoring the content of working memory (Perret, 1974; Troyer *et al.*, 1997; Unsworth *et al.*, 2011). In the naming task, the participant was asked to provide the name of each of the 40 black and white pictures displayed one by one on a computer screen. The participants gave their response orally, and the examiner wrote down and scored their responses. The semantic matching task was adapted from the Pyramids and Palm Trees Test (Howard and Patterson, 1992). In each trial, three words were presented on the computer screen, with the target word presented above the other two words. For each triad, participants were asked to select, through finger pointing, the bottom item that was semantically related to that at the top (the target). Among the bottom items, one was linked to the target with a functional or a category relationship; the other item was a semantic

distractor. A total of 40 trials was performed and scored. The naming and semantic matching tasks aimed to ensure the absence of semantic memory deficits in our patients [i.e. scores ≥ 37 correct responses on the naming task and 38 on the semantic matching task (Merck *et al.*, 2011)].

The participants also underwent the short version of the Torrance test, a divergent thinking test, to assess creative abilities based on a well-validated test (Goff and Torrance, 2002).

Experimental tasks

Combined Associates Task

See Supplementary material (Method 1) and Bendetowicz *et al.* (2017) for detailed information on this task.

We built a new verbal task adapted from Mednick's remote associates task (Mednick, 1962), in which subjects were required to find a word related to all three cue words that were presented to them when there was no obvious link between these cue words. The construct validity and reliability of the remote associate task has been shown in previous studies (Mednick, 1962; Mednick *et al.*, 1964a; Chermahini *et al.*, 2012). Performance on such tasks depends both on the organization of spontaneous associations between words or concepts (associative thinking), and on the constrained generation and combination of remote associates, likely using controlled processes (as detailed in Table 2; Mednick *et al.*, 1964a; Ward and Kolomyts, 2010; Chermahini *et al.*, 2012; Benedek and Neubauer, 2013; Lee and Theriault, 2013; Kenett *et al.*, 2014; Jones and Estes, 2015).

Based on the hypothesis that the more remote the elements to combine, the more creative the process (Mednick, 1962), we adapted the remote associates task and varied the semantic distance between the written cue words and the solution word(s). We used free association norms to quantify mean associative distance (association strength; Debrenne, 2011; <http://dictaverf.nsu.ru/>) between the cue words and the solution word(s) for each trial. We built 72 CAT trials and classified the trials according to the median of the association strength. Thirty-six trials with mean association strength greater than the median (>7) were classified as 'close CAT' trials [for example, 'rue' (street), 'campagne' (countryside), 'centre' (centre); the solution is 'ville' (town)]. Thirty-six trials were classified as 'distant CAT' trials [e.g. 'pont' (bridge), 'social' (social), 'attacher' (to tie); the solution is 'lien' (link)]. A previous study showed that healthy participants performed close trials significantly more accurately and with

shorter reaction times than distant trials (Bendetowicz *et al.*, 2017).

The three cue words were displayed on the screen until the participants produced a response, within a time limit of 30 s. After giving their response, participants provided ratings on insight (by pressing V/N keys on the keyboard for yes/no 'Eureka' experience) as it is commonly assessed in the remote associate task, and as detailed in the Supplementary material, and in Bendetowicz *et al.* (2017).

The percentage of trials solved was measured (CAT-solving) for all trials and separately for close and distant trials. To obtain a score that would be more specifically related to the creative potential than to a global solving performance, an index (CAT-index) was calculated as the difference between performance on close and distant trials, divided by the mean performance in both conditions. This index operationalizes Mednick's hypothesis ('the more remote the elements to be combined, the more creative the process or solution'), as distant trials involve a solution that is more distant from the elements to be combined than close trials. Hence, CAT-distant and CAT-close conditions are both remote associate tasks, but correspond to high and low creative conditions, respectively. The CAT-index reflects the ability to solve distant trials (the more creative condition) when controlling for performance in the less creative condition (close trials). In particular, the CAT-index measure allows one to control for processes such as word reading and understanding, vocabulary and lexical retrieval and verbal response selection and production, sensorimotor processing, and the overall ability to solve problems. Importantly, CAT-index also controls for the effects of lexical frequency (of cue and solution words) and word salience (or steepness inducing fixation) of the cue words, which are essential factors influencing remote word associate tasks (Mednick *et al.*, 1964a; Gupta *et al.*, 2012; Klein and Badia, 2015) (Supplementary material). Correlation analyses in healthy controls have previously indicated that the CAT-index was related to other creativity measures (Bendetowicz *et al.*, 2017).

Free Generation of Associates Tasks

See Supplementary material (Method 2) for detailed information on this task.

FGAT were free word generation tasks. On each FGAT trial, a cue word was displayed on a computer screen, and the participants were asked to produce another word in response to the cue word according to two conditions, a 'first' and a 'distant' condition.

Table 2 Task requirements in terms of cognitive processes or mechanisms

	FGAT-first	FGAT-distant	CAT
Spontaneous semantic associations	+	+	+
Low cognitive control			
Generation of remote associates	–	+	+
Involving controlled retrieval of semantic elements, inhibition of usual and inappropriate associates, selection among the retrieved associates, working memory			
Combination of remote associates	–	–	+
Involving relational integration, multitasking and subgoal integration, branching, evaluation and selection of candidate solutions to meet the constraints of the task, updating and switching in working memory			

In the ‘distant’ condition (FGAT-distant), the participants were asked to say aloud a word that was unusually associated with the cue word, with an original but existing link between the cue word and their response. FGAT-distant aimed to assess the ability to intentionally generate unusual word associations. The uncommonness of responses in a word-to-word generation task with the instruction to be creative has been found to be a reasonably strong correlate of creative performance. Other studies have used similar tasks in which participants were presented with a noun and were asked to say a verb related to the noun, with the instruction to think creatively. Lower semantic similarity or higher semantic distance of the noun–verb pairs correlated positively with a creativity factor derived from a battery of measures, including achievement-based measures (Green *et al.*, 2012a, 2015; Prabhakaran *et al.*, 2013). Overall, both the CAT and FGAT-distant tasks were creativity-related tasks and involve the ability to generate remote associations, while the CAT additionally requires combination processes (Table 2).

In contrast, the ‘first’ condition or FGAT-first was not a creativity task but was aimed to assess to what extent semantic associations were common, typical (or ‘steep’ according to Mednick’s hypothesis) in individuals. In the FGAT-first condition, the subjects were asked to say aloud the first word that came to mind. This condition involved associative thinking with minimal control demands.

The same list of 58 words was used in the first and the distant conditions (Supplementary material). We measured the frequency or commonness of the responses of each participant, relative to normative data from 96 healthy subjects (‘FGAT-first/distant frequency’) as the main FGAT measure. We also measured the uniqueness (percentage of responses that were not given by subjects from our normative data: ‘FGAT-first/distant unique responses’) and the typical nature [percentage of responses that corresponded to the first associate of the cue word according to French association norms (Debrenne, 2011): ‘FGAT-first/distant typical responses’] of the patients’ responses.

Testing and procedure

The tasks were programmed using MeyeParadigm [e(ye)Brain Inc., 2009] running on a PC. Participants performed the FGAT-first before the FGAT-distant condition for duration of about 10 min. The CAT task was performed thereafter. After the instructions of the CAT task, participants were trained on 10 trials and then performed the 72 test trials for a total duration of ~40 min.

Statistical analyses

Statistical analyses were performed using SPSS software (v22.0; IBM Corp.). Between-group differences were analysed using parametric *t*-tests when the assumption of normality was met or non-parametric tests otherwise, using exact *P*-values for comparison within our patient group. Scores were *Z* transformed to compare the performance across CAT and FGAT tasks. The alpha-level used to determine significance was set to 0.05.

Neuroimaging analyses

Imaging lesion preprocessing

Patients underwent a high-resolution T₁-weighted MRI acquisition that was spatially normalized to the Montreal Neurological Institute (MNI) template using the ‘unified segmentation’ approach combined with a lesion masking to limit the impact of a brain lesion on the spatial normalization (Crinion *et al.*, 2007; Andersen *et al.*, 2010; Ripollés *et al.*, 2012). Lesions were manually segmented on the normalized MRIs by trained neurologists. The resulting lesion volumes in the MNI space were used for further analyses. The lesions of all the patients overlapped on a brain template are displayed in Supplementary Fig. 1. The lesion method has been used previously (Urbanski *et al.*, 2016) and is detailed in the Supplementary material (Method 3).

Lesion-deficit mapping approach

To investigate lesion-deficit relationships, we ran a VLSM analysis (Bates *et al.*, 2003) using the NPM software (<http://www.nitrc.org/projects/mricron>). This approach statistically compares for each voxel the performance of the patients damaged in that voxel to those of other patients. We used the non-parametric Brunner-Munzel test. VLSM results were reported with a significance threshold of $P < 0.05$ with a family-wise errors (FWE) correction for multiple comparisons using permutations. Given the small number of patients, we prioritized a larger coverage with a permissive minimal overlap threshold of three lesions, i.e. only the voxels having a lesion overlap from at least three patients were considered. Seventy-two per cent of the prefrontal cortex was concerned by at least one lesion, but the percentage of prefrontal voxels that satisfied the three overlaps threshold was 36% (Supplementary material, Method 4). We also report the results of the VLSM analysis when using a higher overlap threshold of four lesions in the Supplementary material. Separate VLSM maps were run for the two tasks related to creative thinking: FGAT-distant and CAT-index. Subsequent group comparison analyses were performed to examine the specificity of the deficits according to the critical lesion locations revealed by the VLSM analyses. In this analysis, patient groups were selected from the VLSM analysis based on their deficit on either the CAT-index or the FGAT-distant score, and were compared to other patients and to each other regarding their demographic characteristics and performance in the other cognitive tasks. Although this selective analysis can be biased by its lack of independence from the VLSM study, it allowed directly comparing the impact of critical lesion locations when looking for an interaction between tasks and lesion location.

Impact of disconnections: a disconnection-deficit mapping approach

To explore the impact of tract disconnection on creative performance, we used a disconnection-deficit approach by calculating the probability of disconnection of white matter tracts caused by each lesion, using Disconnectome maps software (Thiebaut de Schotten *et al.*, 2015) as part of the BCBtoolkit (<http://www.bcbtoolkit.com>). For each patient, a disconnectome map was obtained by diffusion-based tractography of white matter fibres passing by the lesion. Tractography was performed in a group of 10 healthy controls. First, lesions were

registered to the diffusion images of the group of healthy controls (Rojkova *et al.*, 2016) using affine and diffeomorphic deformations (Klein *et al.*, 2009; Avants *et al.*, 2011). The registered lesions were used as seed points to track streamlines passing through the damaged regions in each healthy dataset. For each patient, we created a binary visitation map of the streamlines intersecting the lesion. These maps were normalized to MNI space using the inverse of the deformations mentioned above. We created percentage overlap maps by summing at each point in MNI space the normalized visitation map of each subject; hence, the value in each voxel of the visitation maps varied according to intersubject variability. For each lesion we obtained a disconnectome map that approximates the disconnections provoked by the lesion of each patient with a probability of disconnection >50% (disconnectome page on <http://toolkit.bcblab.com/>). Then we enter these maps in a regression analysis in FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) to examine the disconnections that were associated with a deficit. Age, years of education, and lesion volume were covaried out.

Impact of damage to the default mode and the fronto-parietal control networks

Based on the functional imaging literature, we hypothesized that patients with a lesion affecting the DMN and/or the FPCN would have a creativity loss. To test this hypothesis, we examined how damage to these networks impacted the patients' performance. We used the functional networks described by Smith *et al.* (2009) to define the DMN and FPCN (Supplementary Fig. 2). We determined for each patient if his/her lesion damaged these functional networks using FSL routines (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>) in the MNI152 space. The functional networks from Smith *et al.* (2009) were arbitrarily thresholded at a conservative $z = 4$ (a threshold that these authors also used in their original paper). Each of the networks was considered as damaged if at least 1% of the network was affected by the lesion to avoid considering a network as damaged when only a few voxels of the lesion were overlapping it. The main creativity measures, CAT-index and FGAT-distant frequency scores, in the patients with damaged versus intact networks were compared statistically (Table 4 and Supplementary Fig. 3). As lesions often overlapped with more than one network, the impact of damage to the distinct resting state networks could not be directly compared to each other.

Results

Behavioural analyses

Compared to controls, patients had significantly lower scores on the CAT, especially when the words to combine were more distant (assessed based on a CAT-index score). In patients, there was no significant correlation between CAT performance and age [$r = -0.109$, not significant (ns)], lesion volume ($r_s = -0.351$, ns) and lesion delay ($r = 0.059$, ns). In patients, there was no significant correlation between CAT-index and phonemic fluency ($r = -0.345$, ns), category fluency ($r = -0.054$, ns), Stroop

interference ($r = -0.338$, ns), naming task ($r_s = -0.271$, ns) and semantic matching task ($r_s = 0.145$, ns). CAT-index did not correlate with response times in the FGAT conditions (FGAT-first-reaction times: $r_s = 0.001$, ns; FGAT-distant-reaction times: $r_s = -0.059$, ns).

The commonness of the words produced in the FGAT-first and FGAT-distant conditions was not significantly different between the patient and control groups (Supplementary Table 2). There was also no significant correlation between the commonness of the patient responses in the FGAT-distant and -first frequency scores and age (first: $r_s = -0.196$, ns; distant: $r = 0.118$, ns), lesion volume (first: $r_s = 0.232$, ns; distant: $r_s = 0.296$, ns) and lesion delay (first: $r_s = 0.113$, ns; distant: $r = 0.155$, ns). There was no significant correlation in patients between the FGAT-first and -distant frequency scores and phonemic fluency (first: $r_s = -0.091$, ns; distant: $r = -0.282$, ns), category fluency (first: $r_s = 0.028$, ns; distant: $r = -0.237$, ns), Stroop interference (first: $r_s = -0.062$, ns; distant: $r = -0.351$, ns), naming task (first: $r_s = -0.096$, ns; distant: $r_s = -0.077$, ns) and semantic matching task (first: $r_s = 0.286$, ns; distant: $r_s = 0.167$, ns).

These results indicate that our experimental measures were not correlated with scores on control tasks measuring the inhibition of prepotent responses, fluency processes and semantic memory.

In healthy controls, the uniqueness of responses provided in the FGAT-distant condition correlated with the originality and fluency scores on the Torrance test ($r = 0.339$, $P = 0.015$; $r = 0.317$, $P = 0.023$), and the CAT-index score correlated with the originality scores on the Torrance test ($r = -0.282$, $P = 0.045$). These results suggest that FGAT-distant and CAT-index are related to creativity as assessed by divergent thinking tasks.

Lesion-deficit mapping analyses

VLSM statistics revealed specific frontal regions responsible for lower creative abilities. One such region was located in the left rostrolateral prefrontal cortex [rIPFC; volume 0.23 cm^3 ; Brodmann area (BA) 10; MNI coordinates $x = -30$, $y = 50$, $z = 2 \text{ mm}$; $P < 0.05$, FWE-corrected] that was associated with a significant deficit on the CAT, especially for distant trials (CAT-index; Fig. 1A and Supplementary Fig. 4). Damage to this region impaired the ability to combine remote semantic associations, but its effect on the ability to generate remote associates (FGAT-distant) was not significant (Table 3). Additionally, the right rostromedial region [rostromedial prefrontal cortex (rmPFC); volume 0.38 cm^3 , BA 10/11; MNI coordinates $x = 12$, $y = 43$, $z = -6 \text{ mm}$; $P < 0.05$, FWE-corrected] was critical for generating distant associates, as patients with a lesion in this region produced more common and less unique responses in the FGAT-distant condition than other patients (Fig. 1B). Importantly, patients with a lesion in the right rmPFC produced more common and less unique responses in the FGAT-first condition than did

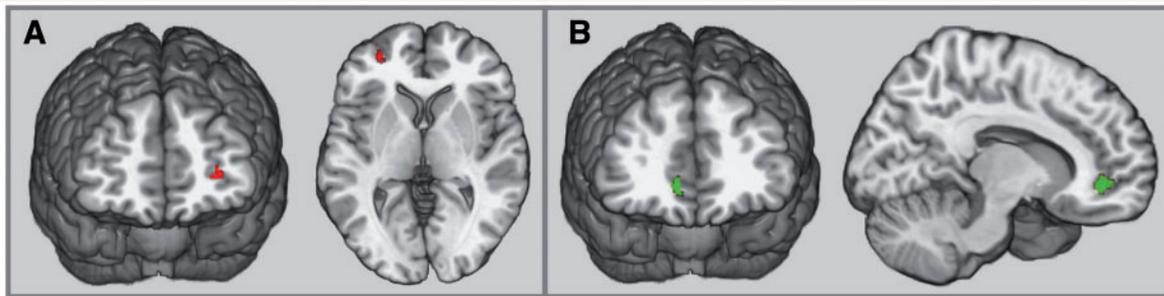


Figure 1 Lesion-deficit mapping associated with CAT-index and FGAT-distant performance. Coloured clusters show the lesion location associated with a significant impairment on the CAT-index (red) (A) and on the FGAT-distant condition (green) (B) ($P < 0.05$, FWE-corrected).

Table 3 Descriptive data and experimental task performance according to lesion location, along with statistical comparisons of the three groups of patients

	Left rIPFC lesion (n = 6) ^a	Right rmPFC lesion (n = 6) ^a	Other patients (n = 16)	Left rIPFC versus other patients groups	Right rmPFC versus other patient groups
Descriptive data: mean (SD)					
Age (years)	52.8 (18.1)	42.8 (12.2)	47.1 (15.6)	$t(20) = 0.743, P = 0.466$	$t(20) = -0.589, P = 0.563$
Education (years)	13.0 (6.4)	12.8 (2.5)	15.1 (2.5)	$t(20) = -1.150, P = 0.264$	$t(20) = -1.903, P = 0.072$
Lesion volume (cc)	50.6 (51.4)	31.6 (13.4)	25.5 (24.5)	$t(20) = 1.572, P = 0.132$	$t(20) = 0.573, P = 0.573$
Lesion delay (months)	66.7 (43.3)	47.3 (43.2)	53.5 (48.9)	$t(20) = 0.578, P = 0.569$	$t(20) = -0.271, P = 0.789$
Neuropsychological data: mean (SD)					
FAB (/18)	15.7 (1.4)	15.2 (2.3)	15.9 (1.5)	$U = 40.5, P = 0.590$	$U = 42, P = 0.693$
Category fluency (animals)	31.3 (7.7)	27.7 (8.0)	27.7 (7.7)	$U = 37.5, P = 0.449$	$U = 47.5, P = 0.971$
Phonemic fluency (letter P)	22.0 (7.5)	18.2 (6.6)	19.8 (7.0)	$U = 45.5, P = 0.858$	$U = 41, P = 0.641$
Short naming (/40)	39.2 (1.2)	38.7 (1.0)	39.0 (1.1)	$U = 43.5, P = 0.747$	$U = 38, P = 0.494$
Short PPT (/40)	39.3 (0.5)	39.8 (0.4)	39.3 (0.9)	$U = 43.0, P = 0.747$	$U = 33.5, P = 0.294$
Stroop conflict	32.5 (7.4)	37.0 (9.9)	37.4 (9.4)	$U = 29.0, P = 0.178$	$U = 45.0, P = 0.858$
Creative combination task					
CAT-index	41.5 (18.3)	35.6 (10.9)	20.5 (12.8)	Significant based on the VLSM analysis	$t(20) = 2.547, P = 0.019$
CAT-solving (close trials)	47.7 (10.6)	50.0 (11.5)	51.0 (10.7)	$t(20) = -0.655, P = 0.520$	$t(20) = -0.199, P = 0.844$
CAT-solving (distant trials)	20.4 (9.7)	23.6 (5.8)	34.4 (11.1)	$t(20) = -2.714, P = 0.013$	$t(20) = -2.240, P = 0.037$
CAT-omissions	11.3 (11.6)	20.6 (21.3)	17.3 (15.6)	$U = 39.5, P = 0.541$	$U = 42.0, P = 0.693$
Creative generation task					
FGAT-distant (frequency)	3.15 (1.34)	4.75 (1.07)	3.13 (1.04)	$t(20) = 0.033, P = 0.974$	Significant based on the VLSM analysis
FGAT-distant (typical responses)	5.0 (4.5)	9.5 (6.5)	5.3 (4.9)	$t(20) = -0.109, P = 0.914$	$t(20) = 1.659, P = 0.113$
FGAT-distant (unique responses)	30.0 (12.1)	17.5 (7.2)	29.3 (8.2)	$t(20) = 0.154, P = 0.879$	$t(20) = -3.108, P = 0.006$

The impact of the two lesion locations identified in the VLSM analyses (left rIPFC associated with CAT and right rmPFC associated with FGAT) was further explored in *post hoc* analyses to better characterize the cognitive profile of the patients. Based on the VLSM results of CAT-index and FGAT-distant frequency scores, patients were distributed into three groups according to their lesion location: patients with a lesion affecting the left rIPFC VLSM region ('left rIPFC group'), patients with a lesion in the right rmPFC region ('right rmPFC group'), and patients with a lesion that preserved these two regions ('other patients group'). The three groups did not differ significantly in terms of age, years of education, lesion volume or lesion delay. Note that some of the statistics reported for the generation and the combination tasks may be subject to a selection bias and were not used to draw conclusions.

^aOne patient with a lesion affecting both the rIPFC and the rmPFC regions has been removed from these analyses.

Results are shown as the means (SD) or mean percentages of correct responses (SD) for experimental tasks. 'CAT-solving' refers to the percentage of correct responses in the CAT task, and is reported separately for close and distant trials. 'CAT-omissions' refers to the percentage of omissions among failed trials (the remaining failed trials were trials in which participants provided incorrect solution words). Exact *P*-values significant at $P < 0.05$ are provided.

patients with a spared right rmPFC (Fig. 2 and Supplementary Table 3). Patients with a right rmPFC lesion did not differ from other patients in performance on the conflict condition of the Stroop test (Table 3) or in mean reaction times in the FGAT-first and FGAT-distant

trials (Supplementary Table 3), which indicated that they did not experience inhibition difficulties or impulsive behaviours. Hence, the impairment of the rmPFC patients in the creativity-related tasks could not be entirely explained by a lack of response inhibition or by increased impulsivity.

In addition, patients with a right rmPFC lesion had slightly (but not significantly) longer reaction times in FGAT-first trials but shorter reaction times in FGAT-distant trials, which does not argue for energization difficulties (the process of initiation and sustaining of any response; [Stuss and Alexander, 2007](#)). These findings suggest that a right rmPFC lesion impacts spontaneous semantic associations (FGAT-first) as well as the voluntary generation of remote associations (FGAT-distant). Additionally, patients with a right rmPFC lesion were also impaired in the CAT task ([Table 3](#)).

To better understand the consequences of the two lesion locations, we ran a mixed ANOVA comparing CAT-index and FGAT-distant commonness Z-scores between the 'left rlPFC' and 'right rmPFC' groups [patients with left rostralateral prefrontal cortex (rlPFC) versus right rmPFC lesions], using lesion volume, age, and years of education as covariates ([Fig. 2](#)). Although this analysis allowed us to directly compare the impact of different lesion locations on different tasks, it may be subject to a selection bias, since the patient groups were formed based on the VLSM regions. Hence, the results will be interpreted with caution and in integration with the other findings of the study. The ANOVA showed no significant task effect [$F(1,7) = 1.299$, ns] and no significant group effect [$F(1,7) = 0.158$, ns] but did show a significant interaction between tasks and groups [$F(1,7) = 5.766$, $P = 0.047$]. Left rlPFC and right rmPFC lesions both impacted the CAT but only a right rmPFC lesion was associated with difficulties in the FGAT task ([Table 3](#) and [Fig. 2](#)).

Finally, there was no significant difference between patient groups in Stroop scores, verbal fluency scores, naming and semantic matching scores ([Table 3](#)). The lesion overlap of each patient group is provided in [Supplementary Fig. 5](#).

Overall, these results show that different lesion locations were associated with different profiles of performance in generation and combination tasks, suggesting that left rlPFC and right rmPFC lesions affect different brain mechanisms involved in creativity. As shown in [Fig. 2](#), patients with a right rmPFC lesion were impaired in both creativity-related tasks (generation in the FGAT-distant, combination in the CAT) and produced more common associates in the spontaneous word association task (FGAT-first), whereas patients with a left rlPFC lesion were impaired in the CAT only.

Disconnection-deficit mapping analyses

The disconnection-deficit mapping method showed that the disconnection of tracts connecting the left rlPFC was associated with difficulties in combining remote ideas (CAT), especially when connections from the left anterior thalamic radiations and the left fronto-marginal tract were disconnected ([Fig. 3A](#); $P < 0.05$, FWE-corrected). This result remained significant when the FGAT-distant frequency score

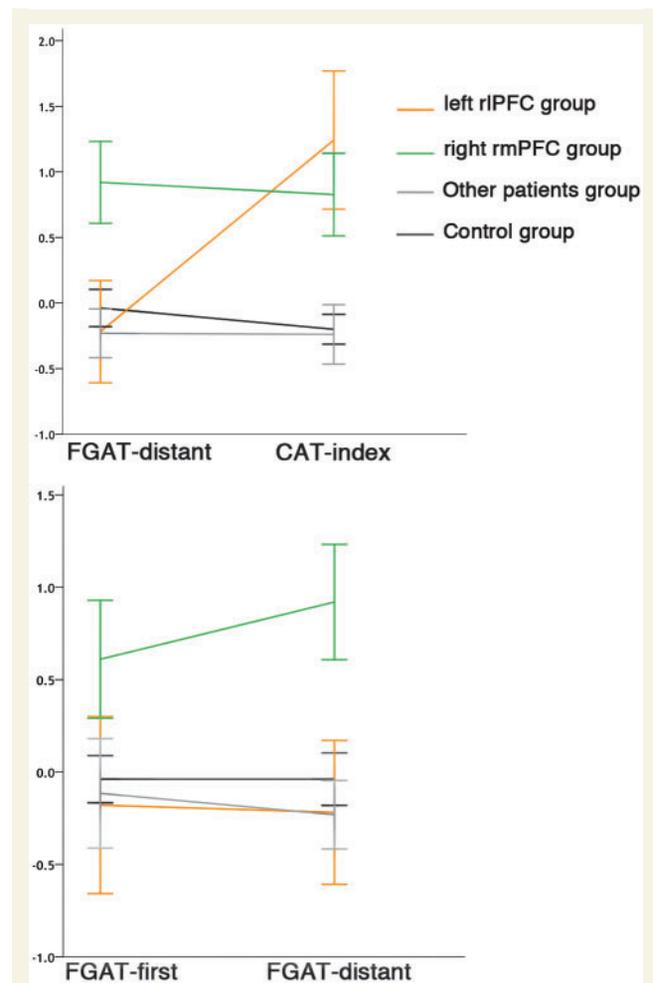


Figure 2 Post hoc analysis of CAT and FGAT performance in the distinct patient groups. Patients in the 'left rlPFC group' had a lesion affecting the left rlPFC as identified in the VLSM analysis; patients in the 'right rmPFC group' had a lesion affecting the right rmPFC as identified in the VLSM analysis. Patients with a lesion that spared these two regions were pooled in the 'other patient group'. The 'control group' included paired healthy subjects. The 'right rmPFC group' showed significantly poorer results than the other groups for both FGAT-distant and CAT-index performance whereas patients in the 'left rlPFC group' were only impaired in the CAT-index (*top*). Patients in the 'right rmPFC group' generated more common responses than any other group in the FGAT-distant and FGAT-first conditions (*bottom*). Error bars represent standard errors. Note that the higher the FGAT scores were, the more common the responses of the participants, and the higher the CAT-index scores were, the poorer the creative performance. Y-axes: performance expressed as Z-scores.

was entered as a covariate in the regression, indicating that the deficit in CAT-index associated with the reported disconnections was not related to a deficit in the FGAT-distant task.

In contrast, the difficulties in generating distant ideas (FGAT-distant frequency) were associated with a disconnection of the right cingulate fasciculus ([Fig. 3B](#); $P < 0.01$, not surviving FWE correction).

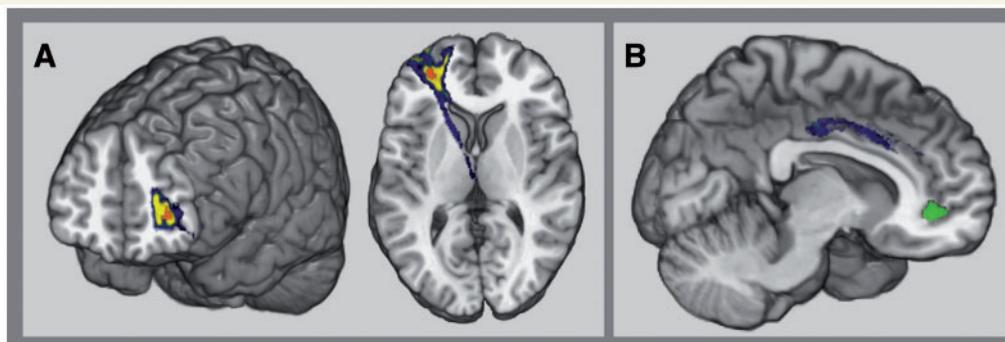


Figure 3 Disconnection-deficit mapping. The disconnection-deficit map of the CAT-index score ($P < 0.05$, FWE-corrected) (A) and of the FGAT-distant commonness of responses ($P < 0.01$, uncorrected) (B) are superimposed on a 3D brain rendering and displayed in a blue-to-green gradient. The VLSM regions associated with CAT-index and FGAT-distant commonness are superimposed in red and green, respectively.

Table 4 Demographic data, experimental task performance, and statistical comparisons of the three groups of patients as a function of the integrity of the default mode and the fronto-parietal control networks

	Damaged DMN (n = 9)	Intact DMN (n = 20)	Damaged left FPCN (n = 10)	Intact left FPCN (n = 19)	Damaged right FPCN (n = 12)	Intact right FPCN (n = 17)
Descriptive data						
Age (years)	48.8 (13.4)	47.0 (16.2)	50.7 (16.9)	45.8 (14.4)	44.4 (13.7)	49.7 (16.2)
Education (years)	12.7 (2.6)	14.7 (3.9)	13.4 (5.0)	14.4 (2.8)	14.7 (3.3)	13.7 (3.9)
Lesion volume (cm ³)	53.7 (54.9)	28.2 (23.4)	50.5 (53.6)	28.5 (23.0)	50.2 (35.7)*	26.1 (35.7)
Lesion delay (months)	59.4 (45.8)	53.0 (45.1)	74.5 (44.8)	44.7 (42.1)	60.3 (43.0)	51.2 (46.7)
Creative combination task						
CAT-index	36.6 (13.1)	25.8 (17.4)	39.2 (16.3)*	23.9 (14.7)	27.1 (16.7)	30.6 (17.0)
Creative generation task						
FGAT-distant (frequency)	4.3 (1.0)*	3.2 (1.3)	3.6 (1.3)	3.5 (1.3)	4.0 (1.6)	3.2 (1.0)

There was no significant difference between damaged and intact networks for age, education, and lesion volume or delay, except for the right FPCN. Patients with a damaged DMN (compared to patients with intact DMN) produced statistically more common responses in the FGAT-distant task [$t(27) = 2.318$, $P = 0.028$], their performance on the CAT was poorer but not statistically significantly [CAT-index: $t(27) = 1.650$, $P = 0.110$]. Conversely, patients with a damaged left FPCN produced responses in the FGAT task similar to those of patients with intact left FPCN [$t(27) = 0.051$, $P = 0.960$], but their performance on the CAT was significantly poorer [CAT-index: $t(27) = 2.573$, $P = 0.016$]. Performance of patients with a damaged right FPCN did not differ significantly from performance of patients with an intact right FPCN [FGAT task: $t(27) = 1.610$, $P = 0.119$; CAT-index: $t(27) = -0.552$, $P = 0.586$]. Means (SD) are provided. Significant differences between damaged and intact groups are indicated in bold (* $P < 0.05$).

Both results (disconnections associated with CAT-index and disconnections associated with FGAT-distant frequency) remained significant at the same respective thresholds when age, years of education, and lesion volume were not covaried out, and when semantic matching scores and semantic fluency scores were covaried out.

The disconnection-deficit mapping of the FGAT-first score was not significant.

Overall, these results indicate that distinct brain disconnections differently support the ability to freely generate distant associates and the ability to combine these associates.

Resting state network-based analyses

The status of the DMN and FPCN damage for each patient is reported in [Supplementary Table 1](#). We compared the FGAT and CAT performance of the patients with damaged

versus intact networks ([Table 4](#) and [Supplementary Fig. 3](#)). The results confirmed that patients with a damaged DMN had difficulties in generating remote associates (FGAT-distant task; $P = 0.028$), whereas patients with a damaged left FPCN had difficulties in combining remote associates (CAT-index; $P = 0.002$). Damage to the right FPCN did not impair either FGAT-distant or CAT performance. Overall, these results indicate that damage to the DMN and the left FPCN may have a different impact on CAT and FGAT task performance.

Discussion

Based on three complementary methods performed on the same set of data (lesions and scores), the novel findings of this study demonstrate that distinct frontal regions, likely parts of two separate networks, are critical for two aspects

of creative thinking: lesions to the right rmPFC, its connections, or the DMN impaired the ability to generate remote associates, whereas lesions to the left rlPFC, its connections, or the left FPCN impaired the ability to combine remote associates. The cognitive deficits associated with damage to these distinct regions have implications for understanding the associative and controlled processing involved in creative abilities, as discussed below.

Critical role of the right rostromedial prefrontal cortex in generating remote associations: associative thinking mechanisms?

Patients with a lesion in the right rmPFC region had difficulty in generating remote associations in the FGAT-distant condition, and additionally generated more typical responses in the FGAT-first condition, a task that explores spontaneous word associations. Word-association tasks similar to the FGAT-first condition are used to measure semantic distance in association norms, a measure that correlates with the priming effect (Mednick *et al.*, 1964b; Gruszka and Necka, 2002; Faust and Lavidor, 2003). The priming effect estimates how two words or concepts are automatically associated in semantic memory. Hence, more typical word responses in the FGAT-first task may reflect that patients with a right rmPFC lesion have stronger semantic associations, suggesting that they have a different organization or access to semantic associations. Right rmPFC patients performed similarly to the other patient groups in naming, semantic matching and category fluency tasks, and had similar response times under the FGAT conditions, indicating that they had no major impairments or slowness in semantic memory. We can nevertheless not exclude the possibility that patients had a subtle semantic memory impairment that was undetected by the semantic neuropsychological tests that were used. Hence, although the relationships between word association tasks and classical semantic memory tasks—and their related brain networks—remain to be clarified (Bar *et al.*, 2007; Humphreys *et al.*, 2015), our results suggest that the right rmPFC plays a role in associative thinking abilities. Overall, the FGAT-first task is not a creativity task *per se* but reflects associative mechanisms that have been shown to play a role in creative abilities (Merten and Fischer, 1999; Gruszka and Necka, 2002; Faust and Lavidor, 2003; Rossmann and Fink, 2010; Benedek *et al.*, 2012b; Beaty *et al.*, 2014a), and more particularly, computational methods have shown that the organization of semantic memory is related to creativity (Kenett *et al.*, 2014; Benedek *et al.*, 2017).

The differences in the spontaneous access to semantic associations in right rmPFC patients can explain their difficulties in generating distant associates in the FGAT-distant condition. As Mednick stated, ‘if an individual’s associative response to a stimulus element of a creative problem is of

excessive strength, this will tend to reduce the likelihood of occurrence of more remote associative responses . . . and will reduce the probability and speed of creative solution’ (Mednick, 1962). FGAT-distant correlated with the originality and fluency scores on the Torrance test, suggesting this task involves a divergent thinking component. Right rmPFC patients did not differ from other patients in the conflict condition of the Stroop score or in phonemic and category fluency tasks, suggesting that their difficulties in generating remote associates may not be explained by difficulties in inhibition, lexical retrieval, controlled search in memory and working memory. However, as these neuropsychological tasks were not directly matched to the FGAT-distant task, we cannot exclude the possibility that they placed fewer demands on executive processes than FGAT-distant tasks, which could explain the dissociation of performance in these patients. Hence, whether the difficulties of right rmPFC patients in voluntarily generating remote ideas (observed in their FGAT-distant responses) could be solely explained by less flexible spontaneous semantic associations (typicality of their FGAT-first responses) or also by additional semantic control processes required in the FGAT-distant task remains an open question.

The role of the rmPFC in the generation of distant or creative ideas has been shown in a previous lesion study (Shamay-Tsoory *et al.*, 2011) and in functional imaging studies (Seger *et al.*, 2000; Green *et al.*, 2015). Using a word association task, Green *et al.* (2015) found that the generation of unusual associations co-activated the rmPFC and other regions such as the parahippocampal region and the cingulate cortex that are part of the DMN. The current results also showed that damage to the DMN (resting state network analysis) and a disconnection of the cingulate fasciculus (disconnection analysis) altered the free generation of distant ideas (FGAT-distant), suggesting that the rmPFC, as part of the DMN, is critical for the generation of remote ideas. This interpretation is consistent with several morphometry studies in healthy subjects that have shown a link between different structures of the DMN regions and/or the cingulate fasciculus and creativity tasks (Takeuchi *et al.*, 2010; Jung *et al.*, 2013; Chen *et al.*, 2014, 2015; Fink *et al.*, 2014; Kühn *et al.*, 2014; Jauk *et al.*, 2015). Overall, the current results and recent neuroimaging data point to the DMN, especially the core DMN including the rmPFC (Andrews-Hanna *et al.*, 2014; Christoff *et al.*, 2016), as being critical for remote thinking and unusual idea generation.

Furthermore, the poor performance of rmPFC patients on the combination task, CAT, may also be explained by an excessive strength in semantic associations and/or a difficulty in generating distant ideas in the FGAT conditions (Mednick, 1962; Mednick *et al.*, 1964a). A few previous studies have demonstrated that there is a link between the ability to freely generate distant associates (as in the FGAT-distant condition) and creative performance, including performance on Mednick’s task (similar to the CAT;

Rossmann and Fink, 2010; Benedek *et al.*, 2012b; Benedek and Neubauer, 2013; Smith *et al.*, 2013; Hass, 2016). Neuro-computational methods using semantic graphs have also demonstrated that more creative people have more flexible semantic associations (Kenett *et al.*, 2014, 2016; Kenett and Austerweil, 2016; Benedek *et al.*, 2017). Conversely, if a patient is characterized by typicality and excessive strength in semantic associations, when solving the CAT, he/she may be fixated on the strong associates of each cue word, which would prevent the activation of more remote associates and of the solution word (Fig. 4A). Our results support this hypothesis, showing that rmPFC patients had excessively typical spontaneous semantic associations that could explain that they had difficulties to solve the CAT. This interpretation might also be related to the

observation that right rmPFC patients reported more Eureka experiences than the other patients in both correct and incorrect CAT trials (Supplementary Table 4). Indeed, an increased rate of Eureka reports may suggest that these patients rely more than the other patients on strong and spontaneous semantic associations to generate their response. However, this result is difficult to interpret because the link between strong semantic associations and Eureka experiences is not straightforward.

Overall, the deficits in right rmPFC patients support Mednick's hypothesis, which had previously only been explored in healthy subjects, and indicate a role for right rmPFC in associative thinking. This interpretation may not be entirely supported by the resting state network analysis, as patients with DMN damage experienced difficulties in

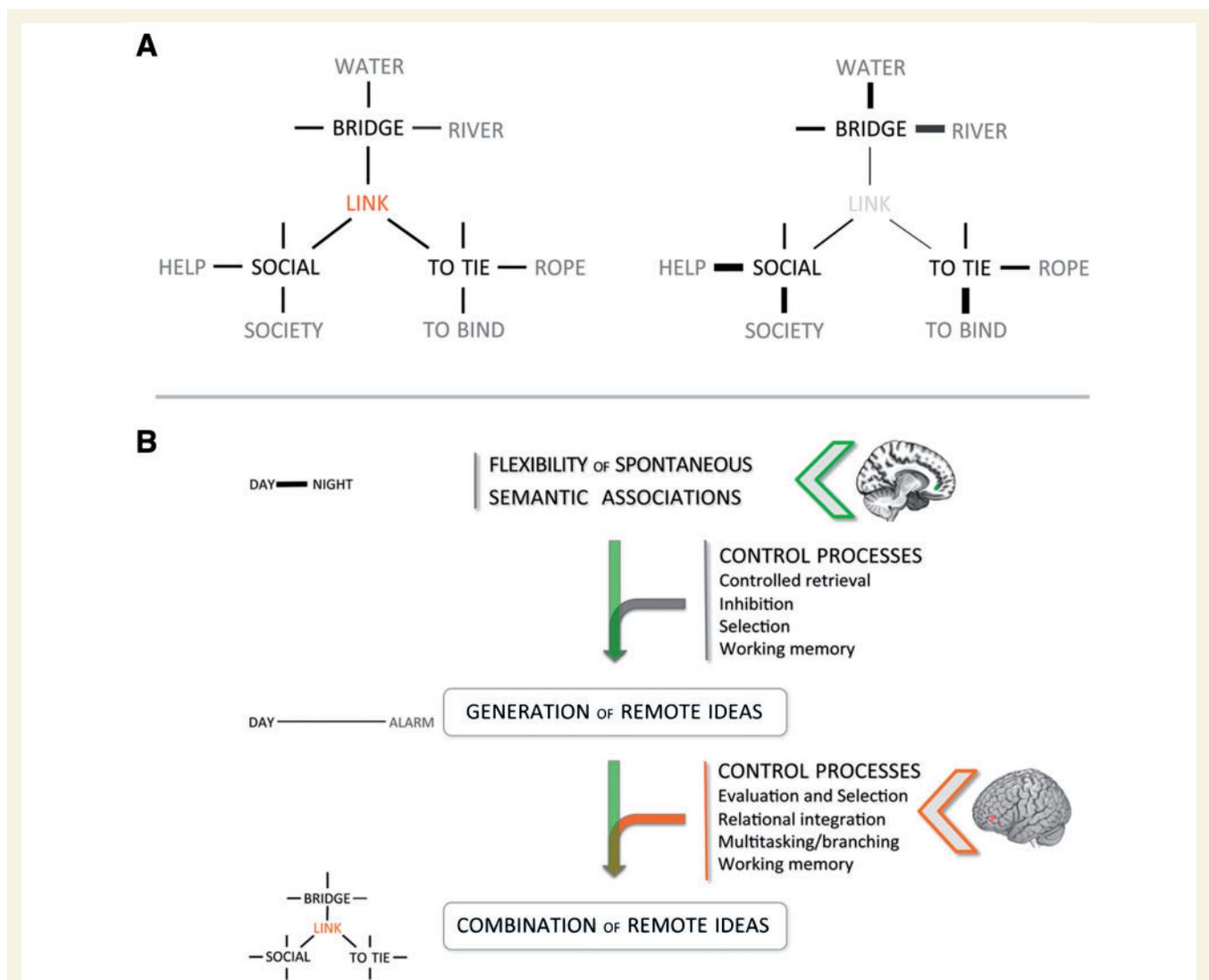


Figure 4 Schematic interpretation of the results. (A) This schematic representation of the CAT illustrates that compared to people with flexible semantic associations (left), patients with typicality in semantic associations (including patients with right rmPFC damage) may be fixated on the strong associates of each cue word when solving the CAT (right, for instance 'river' or 'water' for 'bridge', 'help' for 'social' and 'rope' for 'to tie'). These strong associations prevent the activation of more remote associates, including the solution word 'link'. For instance, if we present a right rmPFC patient with the word 'bridge' he may tend to be restricted to stereotyped responses, such as 'water' or 'river', and would be

generating remote associates (FGAT-distant), although their FGAT-first (spontaneous associations) and CAT-index (combination of remote associates) scores failed to reach significance. However, this interpretation is in line with a growing body of literature showing the role of the DMN in spontaneous cognition (Andrews-Hanna *et al.*, 2010, 2014), in mind wandering and daydreaming (Fox *et al.*, 2015; Christoff *et al.*, 2016), and in contextual associations (Bar, 2009a, b), suggesting its involvement in spontaneous associative thinking. Rather than specific processes or content of thoughts, the DMN may underlie a thinking mode characterized by a spontaneous and associative progression of thoughts that favours creative thinking. A schematic representation of the interpretation of the results according to previous literature is provided in Fig. 4B.

Additional results of this study showed that other cognitive and cerebral mechanisms are necessary for creative combination abilities, as revealed by the cognitive profile of patients with left rIPFC damage.

Critical role of the left rostralateral prefrontal cortex in combining remote ideas

Damage to the left rIPFC impaired CAT performance, whereas the generation of remote associates was preserved. Damage to some of the connections of the left rIPFC, and damage to the left FPCN also impaired CAT performance. This indicates that a left rIPFC lesion altered CAT performance by a mechanism different from that of a right rmpFC lesion (Fig. 4B).

In addition to associative thinking, solving CAT-like tasks indeed involves controlled cognitive mechanisms (Table 2; Mednick, 1962; Lee and Theriault, 2013) such as the strategic search and controlled retrieval in memory (Smith *et al.*, 2013), the inhibition of interference caused by frequent and more salient associates (Gupta *et al.*, 2012), the integration or combination of the retrieved associates (Taft and Rossiter, 1966), and the selection and evaluation of a solution that satisfies the constraints of the task (Mednick, 1962). The preserved FGAT-first performance of left rIPFC patients suggests that they did not have a different organization of semantic associations compared with healthy controls. Their preserved FGAT-distant performance suggests that the controlled processes allowing for the generation of remote associations were also preserved, including controlled retrieval in memory or the inhibition of prepotent associates (Table 3). This interpretation is consistent with the preserved performance of left rIPFC patients in the Stroop interference task and verbal fluency tasks. Hence, a remaining hypothesis is that a left rIPFC lesion (or a disconnection of this region) impacted the CAT performance at the integration or combination step. This integration/combination step likely corresponds to the convergent component identified in recent studies that explored the remote associates task

using computational method and simulations, as opposed to the divergent component (Klein and Badia, 2015; see also Smith *et al.*, 2013).

The role of the left rIPFC in the processes involved in the combination of remote elements remains poorly understood. Only a few functional MRI and EEG studies have been performed using CAT-like tasks, and most of them have focused on the insight component of the task over other information-processing aspects (Jung-Beeman *et al.*, 2004; Sandkühler and Bhattacharya, 2008; Subramaniam *et al.*, 2009; Dietrich and Kanso, 2010). However, two studies support the role of the left rIPFC in creative combination. A meta-analysis of functional imaging studies of creativity showed that the tasks requiring the combination of separate and remote elements, i.e. ‘creative combination tasks’ were associated with more activation in the left rIPFC than other types of creativity tasks (Gonen-Yaacovi *et al.*, 2013). A morphometry study in healthy subjects showed a correlation between creative combination abilities and grey matter volume in the left rIPFC (Bendetowicz *et al.*, 2017). Thus, despite the limitations of the current study (including its small sample size, the non-independence between VLSM and group analyses, and the use of control tasks that were not strictly matched to the experimental tasks), the convergence with previous findings on creativity using different approaches reinforces the strength and interpretations of the current results.

The hypothesis regarding the role of the left rIPFC, and possibly of the FPCN, in the integration or combination of remote elements in our creativity-related task is also consistent with neuroimaging studies from other fields of research. Previous functional imaging studies have established the role of the rIPFC—in connection with the FPCN—in the integration of relational information (Kroger *et al.*, 2002; Krawczyk, 2012; Parkin *et al.*, 2015; Aichelburg *et al.*, 2016; Hobeika *et al.*, 2016), especially in the integration of semantically remote (Green *et al.*, 2012b) or multiple (Christoff *et al.*, 2001; Bunge *et al.*, 2005; Cho *et al.*, 2010) relationships. Relational integration has been shown to depend on the integrity of the left but not right rIPFC in patients (Urbanski *et al.*, 2016). In this regard, it is noteworthy that CAT-like tasks have shown strong correlations with relational reasoning tasks (Chermahini and Hommel, 2010; Lee and Theriault, 2013; Jones and Estes, 2015). Hence, left rIPFC patients may have difficulties in integrating several pieces of information to solve the CAT. This hypothesis is in agreement with the established roles of the rostral PFC in multitasking (enacting the sequence of subgoals required to achieve a behaviour without any cue in the environment to indicate when to switch subgoals) (Burgess *et al.*, 2007, 2009) and in branching (maintaining a subtask in a reversible pending state during the execution of another one) (Hyafil and Koechlin, 2016). These complex types of processing likely occur when solving the CAT (Table 2 and Fig. 4). However, the computation performed to combine remote associates is not yet fully understood (Ward and Kolomyts,

2010; Thagard and Stewart, 2011; Gupta *et al.*, 2012; Smith *et al.*, 2013; Klein and Badia, 2015), and further studies are needed to better understand this computation and its cerebral substrate.

Finally, the disconnection-mapping results revealed that the role of the left rIPFC in creative combination may be supported by its connections through the anterior thalamic radiations and the fronto-marginal tract in the CAT. This suggests that the involvement of the left FPCN in the CAT is supported by cortico-subcortical connections rather than by a direct long-range fronto-parietal system. The anterior thalamic radiations carry association fibres projecting from the thalamus to frontal cortical structures and reciprocal projections to the anterior part of the prefrontal cortex originating from the mediodorsal nucleus, and they are involved in executive functions, working memory and drive (Catani and Thiebaut de Schotten, 2012). The micro-structure of the left anterior thalamic radiations has been reported to relate to creative abilities in healthy subjects (Jung *et al.*, 2010a, 2013). The fronto-marginal tract connects the lateral and the medial portion of the frontal pole (Rojkova *et al.*, 2016); however, the role of this fasciculus in cognition remains undocumented. Overall, in agreement with previous functional MRI and morphometry data, the current results show that the left rIPFC or some of its connections are critical for combining remote associates, and suggest their role in the integration of multiple and remote elements.

Integration of the results with recent functional connectivity studies and existing theories

A recent series of functional connectivity studies has indicated that creative thinking involves dynamic interactions of large-scale brain systems that include the DMN and FPCN, which are usually anti-correlated at rest, but appear to cooperate during creative tasks and artistic performance (Ellamil *et al.*, 2012; Jung, 2014; Beaty *et al.*, 2016; De Pisapia *et al.*, 2016). Previous studies have also shown that the FPCN and the DMN work in interaction to allow deliberate control or constraints on thoughts (Christoff *et al.*, 2009, 2016). Based on this literature, Beaty *et al.* (2016) proposed that creative performance involves both generative functions possibly supported by the default network and the control functions supported by control-related networks. Our findings are consistent with these data and additionally demonstrate the necessary regions within each anatomical network in patients. We showed that the left rIPFC, likely in connection with other FPCN and subcortical regions, plays a role in controlled processes and is possibly involved in the integration/combination of the generated ideas to meet task-specific goals, whereas the right rmPFC, a region of the DMN, is critical for the generation of remote ideas. Moreover, we showed that damage to the right medial prefrontal region

impacted the associative component of idea generation as reflected by spontaneous semantic associations. Hence, the current results add evidence for the concept of associative and controlled interacting modes of creative thinking that is supported by existing psychological and recent neuroimaging data (for reviews see Dietrich, 2004; Gabora, 2010; Jung, 2014; Beaty *et al.*, 2016; Volle, 2017). These interactive thinking modes are likely not unique to creativity but are probably general in cognition, as soon as we control our stream of thought (Christoff *et al.*, 2009, 2016; Spreng *et al.*, 2010; Chen *et al.*, 2013). They may be linked with classical dual-process theories that generally oppose an intuitive-heuristic system (automatic system 1) to a deliberate analytic system (controlled system 2) (Lieberman *et al.*, 2004; De Neys, 2006; Allen and Thomas, 2011; Kahneman, 2011; Evans and Stanovich, 2013; Varga and Hamburger, 2014; Sowden *et al.*, 2015; Cassotti *et al.*, 2016).

The right lateralization of the region associated with spontaneous semantic associations is consistent with the hypothesis of a right hemispheric dominance for coarse coding of semantic associations (Jung-Beeman, 2005; Kounios and Beeman, 2014). This theory emphasizes the importance of right hemispheric structures for the activation, the selection and the integration of coarser semantic elements, whereas left hemisphere structures may be related to fine-grained processing of semantic knowledge by activating smaller semantic fields. In light of this hypothesis, our results suggest that right prefrontal structures are necessary for the activation of larger semantic fields and to generate distant semantic relations. The experimental distinction between associative and controlled processes and their brain correlates may help reconcile some paradoxical results between insight functional MRI studies that emphasized the role of right brain regions in creativity (Jung-Beeman *et al.*, 2004; Kounios and Beeman, 2014) and meta-analyses of functional imaging studies that highlighted the left dominance of brain regions associated with various creativity tasks (Dietrich and Kanso, 2010; Gonen-Yaacovi *et al.*, 2013; Boccia *et al.*, 2015; Wu *et al.*, 2015).

Limitations

The lesion approach in general, and our results in particular, do not take into account the neuroplasticity that occurs after a brain lesion. Patients with lesions from different aetiologies that have distinct time courses and different mechanisms of plasticity have been included in this study. However, we did not find significant differences in performance between aetiologies, as it has previously been shown for executive functions (Cipolotti *et al.*, 2015). Inclusion of various lesion aetiologies allowed us to obtain a broader brain distribution of lesions, especially in the rostral PFC, which is rarely the site of ischaemic strokes. The small number of patients included ($n = 29$) may limit the possibility to identify all the critical PFC regions related to our tasks. We cannot exclude the possibility that the VLSM

analyses missed other critical prefrontal regions or underestimated the size of the critical functional area because of a lack of statistical power in some of the regions and because of only partial coverage of the frontal lobes. We favoured quality over quantity: the selection criteria were restricted to focal and unique lesions in the prefrontal regions (excluding traumatic brain injury that also provokes diffuse axonal lesion). The current study focused on the frontal region based on its importance in the existing literature on creative cognition; however, the necessity of non-frontal brain regions for creative abilities, especially regions belonging to the DMN, the semantic network, and the control-related networks, should be further tested.

In addition, correlations between CAT-index and FGAT-distant scores with divergent thinking measures and creative achievement in control subjects indicate that CAT and FGAT tasks are creativity-related tasks. However, the precise cognitive processes involved in FGAT-distant and CAT tasks, and their relationships with other creativity tasks, will need to be clarified. The respective critical role of the left rIPFC and right rmPFC and their related networks in these creative processes should also be confirmed in a further independent patient study. Furthermore, creativity is a complex construct that is not fully explored by CAT and FGAT tasks that focus on the semantic domain using word associations. Thus, it is possible that other domains of creativity, for instance non-verbal or more ecological creativity tasks, would involve other or additional brain networks.

Conclusions

Recent findings have shown that creative abilities depend on the interaction between the DMN and the FPCN that may support associative and controlled processing of information. Our results converge and add more causal evidence to these findings by showing using verbal creativity-related tasks that there are critical nodes in these networks supporting associative and controlled processing. The integrity of the right rmPFC was shown critical for associative thinking and to generate remote associates, while the integrity of the left rIPFC and some of its connections was critical for constraining this process at the combination step. The precise role of the DMN in the organization or activation of semantic associations is an important question for future research, which could benefit from neuro-computational methods using semantic graphs. Finally, how the current results based on word association tasks can be generalized to various creativity tasks or domains is an essential issue that could be tested in healthy subjects and in patients.

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Supplementary material

Supplementary material is available at *Brain* online.

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