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Two critical brain networks for generation and combination of remote associations

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Abstract

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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Keywords

Creativity ; lesion; disconnection; brain networks ; semantic associations.

Abbreviations list

BA = Brodmann Area ; CAT = Combined Associates Task ; DMN = Default Mode Network ; FGAT = Free Generation of Associates Tasks ; fMRI = Functional Magnetic Resonance Imaging ; FPCN = Fronto-Parietal Control Network ; FWE = Family-Wise Error ; IFG = Inferior Frontal Gyrus ; MFG = Middle Frontal Gyrus ; MMSE = Mini-Mental State Examination ; MNI = Montreal Neurological Institute ; PFC = PreFrontal Cortex ; rlPFC = Rostrolateral PreFrontal Cortex ; rmPFC = Rostromedial PreFrontal Cortex ; RT = Reaction Time ; SFG = Superior Frontal Gyrus ; VLSM = Voxel-based Lesion-Symptom Mapping ; VMPFC = Ventromedial Prefrontal Cortex

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 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.*, 2012*a*; De Dreu *et al.*, 2012; Lee and Therriault, 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.*, 2012*b*; Beaty *et al.*, 2014*a*), 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.*, 1964*a*; 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.*, 1964*a*; Mednick *et al.*, 1964*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 Therriault, 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 inter-individual variability in morphometry (Jung *et al.*, 2010*b*; Takeuchi *et al.*, 2010; Fink *et al.*, 2014; Jung *et al.*, 2013; Zhu *et al.*, 2013; Kühn *et al.*, 2014; Chen *et al.*, 2015; Jauk *et al.*, 2015; Jung *et al.*, 2015) or in functional connectivity (Takeuchi *et al.*, 2012; Beaty *et al.*, 2014*a*; 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.*, 2014*b*; Chen *et al.*, 2014; Pinho *et al.*, 2014; Beaty *et al.*, 2016). 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 (Mednick 1962), which allowed us to estimate the ability to form new combinations between remote associates; 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 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, that can reflect associative thinking abilities. Critical areas predicting performances were revealed using a voxel-based lesion mapping method (VLSM: Bates *et al.*, 2003; Kinkingnehun *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. 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 matching test, as described in Merck *et al.*, 2011) or who were not able to understand task instructions were excluded form 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 (MMSE ≥ 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, in order 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, 3 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 participants. Patients were excluded if they provided less than 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 (CAT; see Supplementary Method 1 for detailed material).

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.,* 1964*a*; 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.*, 1964*a*; Chermahini *et al.,* 2012; Benedek and Neubauer, 2013; Lee and Therriault, 2013; Kenett *et al.*, 2014; Jones and Estes, 2015; Ward and Kolomyts, 2010).

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 (> seven) were classified as "close CAT" trials (for example, "rue" (street) – "campagne" (countryside) - "centre" (centre), which solution is "ville" (town)). Thirty-six trials were classified as "distant CAT" trials (for example, "pont" (bridge) – "social" (social) – "attacher" (to tie), which 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; Supplementary Table 2).

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 Method 1, 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 (Klein and Badia, 2015; Gupta *et al.,* 2012; Mednick, 1964) (Please see Supplementary Method 1). 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 (FGAT) (Supplementary Method 2).

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.

In the "distant" condition or 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 (the studies from Green *et al.*, 2012*a*, Prabhakaran *et al.*, 2013, and Green *et al.*, 2015 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). 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).

On the other hand, 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 (see Supplementary Method 2). 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 minutes. 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 about 40 minutes.

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 in order 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 on Supplementary Fig. 1. The lesion method has been used previously (Urbanski *et al.*, 2016) and is detailed in the Supplementary 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. Given the small sample of the 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. 72% 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 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.bcblab.com). For each patient, a disconnectome map was obtained by diffusion-based tractography of white matter fibers 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 seedpoints 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 larger than 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/) in order to examine the disconnections that were associated with a deficit. http://toolkit.bcblab.com/ 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; 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 results (Supplementary Table 2)

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 ($r = -0.109$, 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 correlated with response times in the FGAT conditions (FGAT-first-RT: r_s = 0.001, ns; FGAT-distant-RT: 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 = .339, *P* = 0.015; r = .317, *P* = 0.023), and the CAT-index score correlated with the originality scores on the Torrance test (r = -.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 results

VLSM statistics revealed specific frontal regions responsible for lower creative abilities. One such region was located in the left rostrolateral prefrontal cortex (rlPFC; volume 0.23 cc; Brodmann Area (BA) 10; MNI coordinates x=-30, y= 50, z= 2 mm; $P < 0.05$, FWE-corrected) that was associated with a significant deficit on the CAT, especially for distant trials (CAT-index; Fig. 1a; 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 (rmPFC; volume 0.38 cc, BA10/11; MNI coordinates x=12, y=43, z=-6 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 patients with a spared right rmPFC (Fig. 2 lower panel; 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 RTs 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 RTs in FGAT-first trials but shorter RTs 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 rlPFC versus right rmPFC lesions), using lesion volume, age, and years of education as covariates (Fig. 2). Although this analysis allowed directly comparing 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; 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 results (Fig. 3)

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 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).

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 results

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; 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 demonstrates 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 rmPFC 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.*, 1964*b*; 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 (e.g., 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.*, 2012*b*; Beaty *et al.*, 2014*a*), 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 voluntary 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.* found that the generation of unusual associations co-activated the rmPFC and other regions such as the parahippocampal region and the cingulate cortex (Green *et al.*, 2015) 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; Fink *et al.*, 2014; Jung *et al.*, 2013; Chen *et al.*, 2014, 2015; 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.*, 1964*a*). 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.,* 2012*b*; 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 (Benedek *et al.*, 2017; Kenett *et al*., 2014; Kenett and Austerweil, 2016; Kenett *et al*., 2016). 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 be 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 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, 2009b), 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 rlPFC damage.

Critical role of the left rlPFC in combining remote ideas

Damage to the left rlPFC impaired CAT performance, whereas the generation of remote associates was preserved. Damage to some of the connections of the left rlPFC, and damage to the left FPCN also impaired CAT performance. This indicates that a left rlPFC 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; Lee and Theriault, 2013; Mednick, 1962) 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 rlPFC 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 rlPFC patients in the Stroop interference task and verbal fluency tasks. Hence, a remaining hypothesis is that a left rlPFC 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 rlPFC in the processes involved in the combination of remote elements remains poorly understood. Only a few fMRI 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 rlPFC 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 rlPFC 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 rlPFC (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 rlPFC, 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 rlPFC - 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.*, 2012*b*) 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 rlPFC 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 Therriault, 2013; Jones and Estes, 2015). Hence, left rlPFC 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; Fig. 4). However, the computation performed to combine remote associates is not yet fully understood (Gupta *et al.*, 2012, Smith *et al.*, 2013; Klein and Badia, 2015; Thagard and Stewart, 2011; Ward and Kolomyts, 2010), 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 rlPFC 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 fibers 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 microstructure of the left anterior thalamic radiations has been reported to relate to creative abilities in healthy subjects (Jung *et al.*, 2010*a*; Jung *et al.*, 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 fMRI and morphometry data, the current results show that the left rlPFC 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 and colleagues proposed that creative performance involve both generative

functions possibly supported by the default network and the control functions supported by control-related networks (Beaty *et al*., 2016). Our findings are consistent with these data and additionally demonstrate the necessary regions within each anatomical network in patients. We showed that the left rlPFC, 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 (Beaty *et al.*, 2016; Jung, 2014; Dietrich, 2004; Gabora, 2010; Volle, 2017 for reviews). These interactive thinking modes are likely not unique to creativity but are probably general in cognition, as soon as we control our stream of thoughts (Christoff *et al.*, 2009; Spreng *et al.*, 2010; Chen *et al.*, 2013; Christoff *et al*., 2016). 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; Sowden *et al.*, 2015; Varga and Hamburger, 2014; 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 fMRI 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 ischemic 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, in 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 rlPFC 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 rlPFC 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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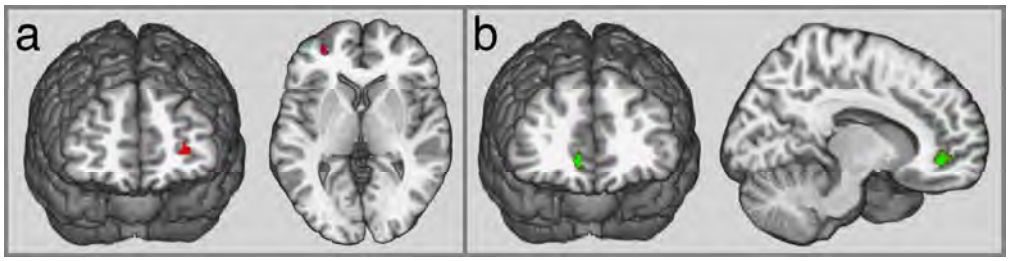
Figure Legends

Fig. 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).

Fig. 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 panel). Patients in the "right rmPFC group" generated more common responses than any other group in the FGAT-distant and FGAT-first conditions (lower panel). 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.

Fig. 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 ($P < 0.001$, 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.

Fig. 4. Schematic interpretation of the results. (a) This schematic representation of the CAT illustrates that compared to people with flexible semantic associations (left panel), 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 panel, 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 characterized as having an associative hierarchy with a steep slope (Mednick, 1962), preventing him/her from getting past the first one or two conventional responses to the stimulus and acceding to the solution. **(b)** Cognitive mechanisms likely affected by a right rmPFC/DMN lesion (green empty arrow) and by a left rlPFC/FPCN lesion (orange empty arrow) and their consequences in further processing for creative activities (green and orange plain arrows). Alteration of associative thinking abilities after right rmPFC damage affects further steps of creative thinking, i.e., on generation and combination mechanisms. Controlled processes, supported in part by the left rlPFC and its connections, manage the generated ideas for further integration and the selection of an appropriate response to satisfy the constraints of the task.



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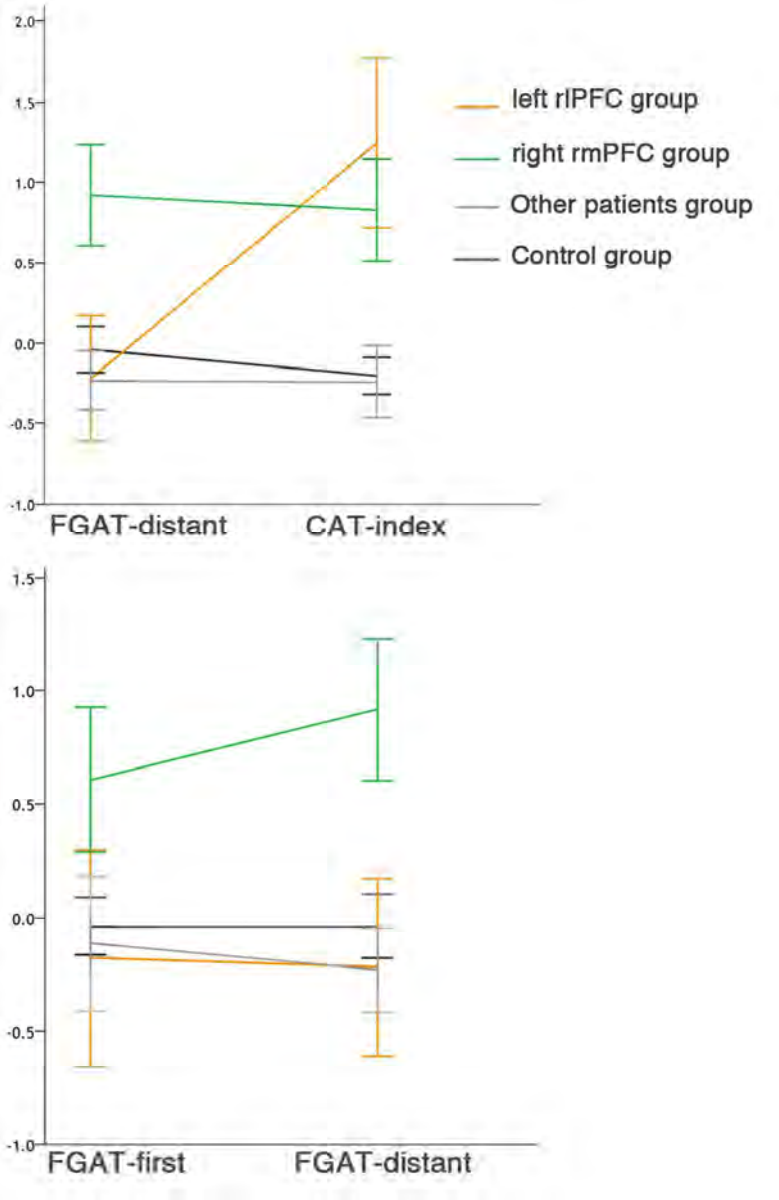
173x43mm (300 x 300 DPI)



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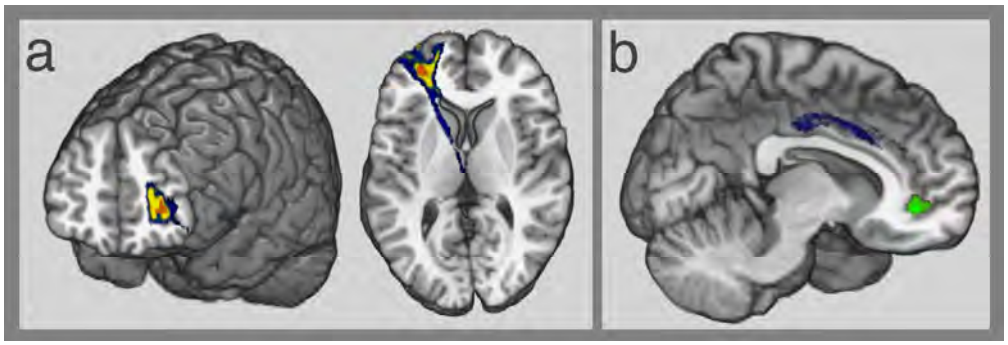

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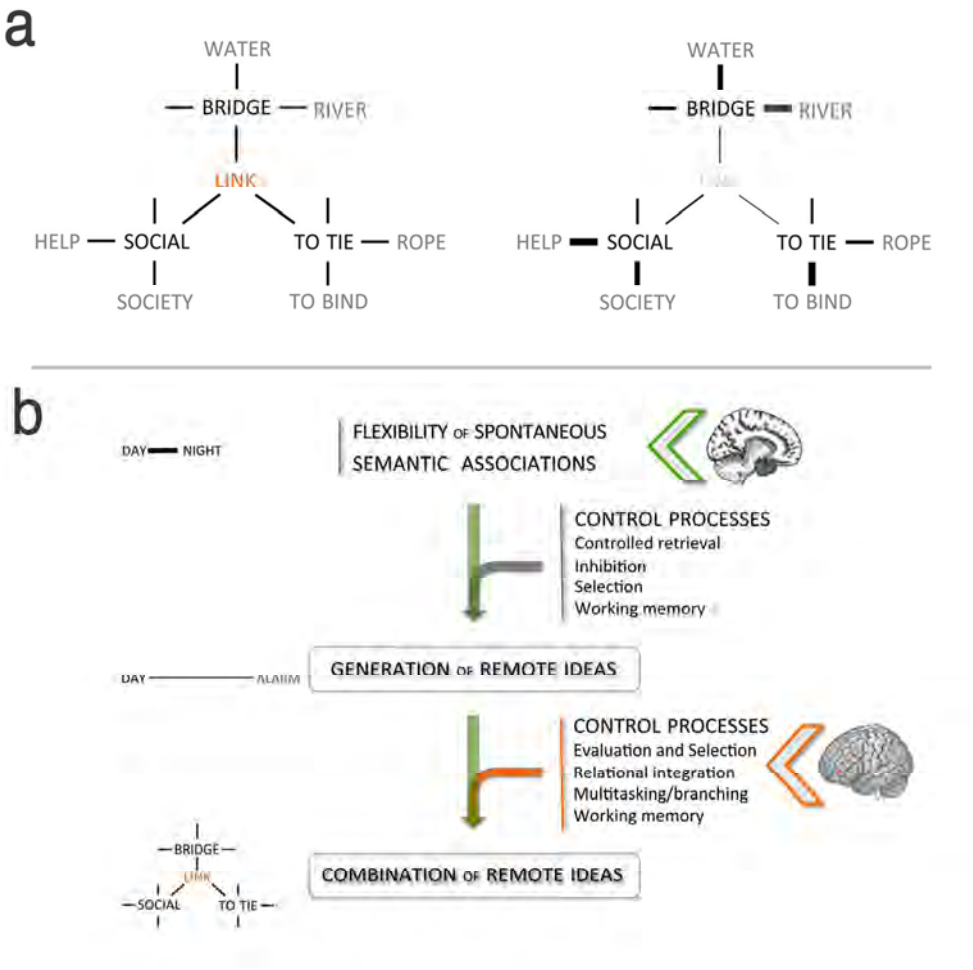

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113x111mm (300 x 300 DPI)

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

Patient	Age (years)	Gender	Education (years)	Etiology	Lesion side	Lesion location
P01	56	F	17	Ischemic stroke	R	Semioval center
P03	46	F	17	Ischemic stroke	L	posterior MFG
P05	64	M	14	Ischemic stroke	R	IFG and MFG
P13	67	M	15	Ischemic stroke	L	anterior IFG
P19	54	M	22	Ischemic stroke	R	IFG / MFG white matter
P27	58	M	12	Ischemic stroke	L	precentral sulcus
P02	55	M	19	Hemorrhage	L	rostral PFC / VMPFC
P07	51	M	11	Hemorrhage	B	rostral PFC
P09	47	M	11	Hemorrhage	R	Cingulate / VMPFC
P10	62	F	13	Hemorrhage	B	Cingulate / VMPFC
P12	46	M	12	Hemorrhage	B	Cingulate / VMPFC

P14	49	M	9	Hemorrhage	B	Cingulate / VMPFC
P16	40	F	22	Hemorrhage	L	rostral PFC
P17	40	M	14	Hemorrhage	B	rostral PFC / VMPFC
P20	71	M	17	Hemorrhage	L	rostral PFC / VMPFC
P25	59	F	16	Hemorrhage	L	VMPFC
P26	26	F	13	Hemorrhage	L	posterior IFG
P29	75	F	12	Hemorrhage	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

Ischemic strokes affected the middle cerebral artery territory. Hemorrhages 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 (P21 & 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. F: female; M: male; R: right; L: left; B: bilateral; IFG: Inferior frontal gyrus; MFG: Middle frontal gyrus; SFG: superior frontal gyrus; vmPFC: ventromedial PFC.

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)	-	-	+

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

	Left rlPFC lesion (n=6)*	Right rmPFC lesion (n=6)*	Other patients (n = 16)	Left rlPFC vs other patients groups	Right rmPFC vs 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 rlPFC associated with CAT and right rmPFC associated with FGAT) was further explored in post hoc analyses in order 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 in 3 groups according to their lesion location: patients with a lesion affecting the left rlPFC VLSM region ("left rlPFC 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. *One patient with a lesion affecting both the rlPFC 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.

Table 4: Demographic data, experimental task performance, and statistical comparisons of the 3 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 (cc)	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 so (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 (*: $\boldsymbol{P < 0.05}$).

Supplementary Table 1

Lesion characteristics and grouping of the patients.

Patient	Interval (months)	Lesion volume (cc)	VLSM group	DMN damaged	Left FPCN damaged	Right FPCN damaged
P01	7	0.27	Other	0	0	0
P02	76	38.87	Left rlPFC group	0	1	0
P03	126	21.22	Other	0	1	1
P04	137	150.85	Left rlPFC group	1	1	0
P05	119	76.63	Other	0	0	1
P06	129	22.43	Other	0	0	1
P07	54	146.42	None*	1	1	1
P08	85	55.60	Left rlPFC group	0	1	0
P09	115	13.79	Right rmPFC group	1	0	0
P10	14	44.12	Right rmPFC group	1	0	1
P11	29	67.13	Other	0	0	1
P12	51	9.29	Other	1	0	0
P13	133	4.71	Other	0	1	0
P14	19	23.17	Right rmPFC group	1	0	1
P15	82	49.67	Right rmPFC group	0	0	1
P16	56	27.59	Left rlPFC group	0	1	0
P17	7	26.71	Right rmPFC group	1	0	0
P18	47	32.13	Right rmPFC group	1	0	1
P19	48	60.11	Other	0	0	1
P20	91	37.06	Other	1	0	0

P21	36	37.79	Other	0	0	1
P22	30	16.45	Left rlPFC group	0	1	0
P23	19	2.95	Other	0	0	0
P24	4	14.81	Other	0	0	0
P25	9	0.87	Other	0	0	0
P26	32	29.19	Other	0	1	0
P27	3	1.22	Other	0	0	0
P29	16	14.21	Left rlPFC group	0	1	0
P30	20	22.11	Other	0	0	1

This table indicates whether the patient's lesion affected the Voxel-Lesion Symptom Mapping (VLSM) regions (rlPFC and rmPFC regions), and the Fronto-Parietal Control Network (FPCN) or the Default Mode Network (DMN) (0: no/ 1: yes).

Left rlPFC: the lesion affected the VLSM region associated with a deficit on the CAT (in the left rlPFC region); right rmPFC: the lesion affected the VLSM region associated with a deficit on the FGAT (in the rmPFC region); other: the lesion spared both VLSM regions. The interval is the delay between the occurrence of the lesion and the inclusion in this study.

* Patient P07 was excluded from post hoc group analyses because his lesion damaged both the left rlPFC and the right rmPFC VLSM regions.

Supplementary Table 2

Descriptive data, neuropsychological scores, experimental task performance in patients and healthy subjects.

	Patients (n=29)	**Healthy subjects (n=54)**	**Group comparisons**
Descriptive data: Mean (SD)			
Age (years)	47.5 (15.2)	45.8 (14.4)	*U* = 741.0, ns
Education (years)	14.1 (3.6)	15.4 (3.0)	*U* = 594.0, ns
Neuropsychological data: Mean (SD)			
MMSE (/30)	27.6 (1.7)	29.0 (0.9)	***U* = 413.0, *P* < 0.001**
FAB (/18)	15.6 (1.8)	16.7 (1.2)	***U* = 473.5, *P* = 0.002**
Category Fluency	28.2 (7.6)	38.1 (8.8)	***t* = 5.10, *P* < 0.001**
Phonemic Fluency	19.6 (7.0)	26.9 (8.1)	***t* = 4.12, *P* < 0.001**
Stroop conflict	35.97 (9.0)	46.3 (11.6)	***t* = -4.167, *P* < 0.001**
Short PPT (/40)	39.5 (0.8)	39.1 (1.3)	*U* = 695.0, ns
Short naming (/40)	39.9 (1.0)	39.0 (1.3)	*U* = 729.0, ns
CAT: Mean % (SD)			
CAT-solving	39.08 (9.66)	48.33 (8.93)	***t* = 4.370, *P* < 0.001**
CAT-index	29.16 (16.69)	21.04 (11.82)	***t* = -2.575, *P* = 0.012**
CAT-Eureka*	87.9 (19.1)	88.7 (9.1)	*U* = 634.5, ns
FGAT: Mean % (SD)			
FGAT-first (frequency)	22.57 (9.33)	21.66 (7.79)	*U* = 700.0, *P* = 0.428
FGAT-distant (frequency)	3.56 (1.31)	3.40 (1.46)	*t* = -0.474, *P* = 0.636

The CAT-solving score represents the percentage of correct responses (for close and distant trials). The CAT-index score represents the performance on close minus distant trials, divided by the mean performance on both trials. Performance on the FGAT is represented by the frequency of the subject's response based on data collected on 96 healthy subjects (50

females; mean age = 44.4 years, SD = 14.9 and mean education = 15.3 years, SD = 3.2). *CAT-Eureka represents the mean percentage of Eureka reports (SD) among correct CAT trials. Results are reported as the means (SD) or mean percentage of correct responses (SD) for the experimental tasks. Exact *P* values significant at $P < 0.05$ are provided. MMSE: Mini Mental State Examination; FAB: Frontal Assessment Battery; PPT: Pyramid and Palm Tree Test.

Supplementary Table 3

Impact of a right rmPFC lesion on FGAT performances.

	Damaged right rmPFC region	**Intact right rmPFC region**	**Damaged vs intact groups comparison**
FGAT-first (frequency)	27.92 (6.37)	20.87 (9.60)	***U* = 36.0, *P* = 0.037**
FGAT-first (typical responses)	25.29 (8.16)	18.55 (9.84)	*U* = 41.0, *P* = 0.067
FGAT-first (unique responses)	9.71 (4.72)	17.50 (11.71)	***U* = 38.0, *P* = 0.046**
FGAT-first RT (ms)	3481 (1229)	3357 (1065)	U = 69.0, ns
FGAT-distant (frequency)	4.88 (1.04)	3.14 (1.1)	***t*(27) = 3.696, *P* = 0.001**
FGAT-distant (typical responses)	9.57 (6.0)	5.18 (4.68)	*t*(27) = 2.026, *P* = 0.053
FGAT-distant (unique responses)	17.57 (6.55)	29.50 (9.10)	***t*(27) = -3.196, *P* = 0.004**
FGAT-distant RT (ms)	6619 (1868)	6760 (2071)	U = 71.0, ns
Stroop conflict score	35.71 (9.62)	36.05 (8.96)	*t*(27) = -0.084, *P* = 0.934

This table provides the means (SD) or mean percentage of correct responses (SD) for the experimental tasks and the Stroop conflict score in patients with damaged and intact right rmPFC. RT: Reaction Time. Exact *P* values significant at $P < 0.05$ are provided.

Supplementary Table 4

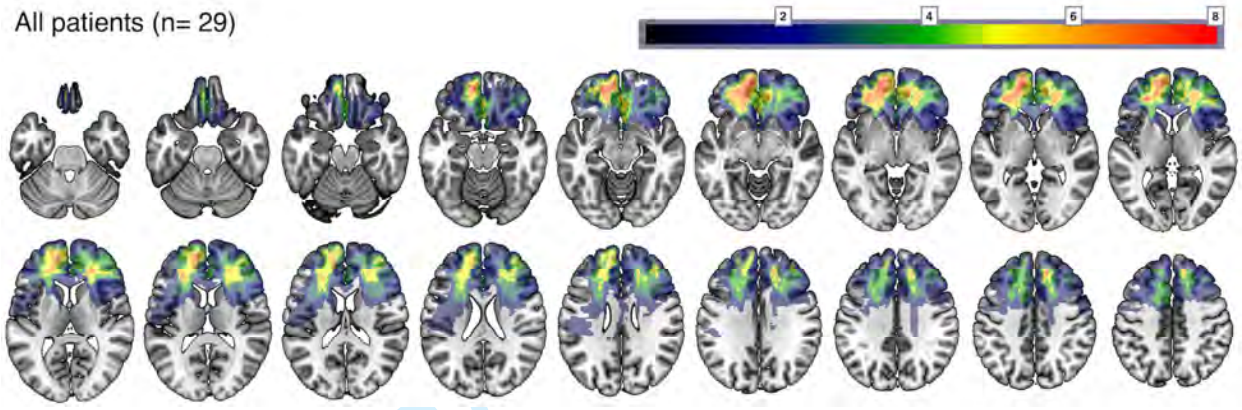
Insight subjective reports in the three groups of patients

	Left rlPFC lesion	**Right rmPFC lesion**	**Other patients**	**Left rlPFC vs other patients groups**	**Right rmPFC vs other patient groups**
CAT-Eureka (%correct trials)	85.6 (16.1)	99.0 (1.6)	84.2 (22.9)	$U = 43$, $P = 0.747$	**$U = 16$, $P = 0.017$**
CAT-Eureka (%incorrect trials)	53.8 (22.7)	90.0 (8.3)	63.8 (23.8)	$U = 34$, $P = 0.302$	**$U = 10.5$, $P = 0.006$**

Results are shown as the mean percentage of Eureka reports (SD) among correct and incorrect CAT trials. Exact *P* values significant at $P < 0.05$ are provided.

Supplementary Fig. 1

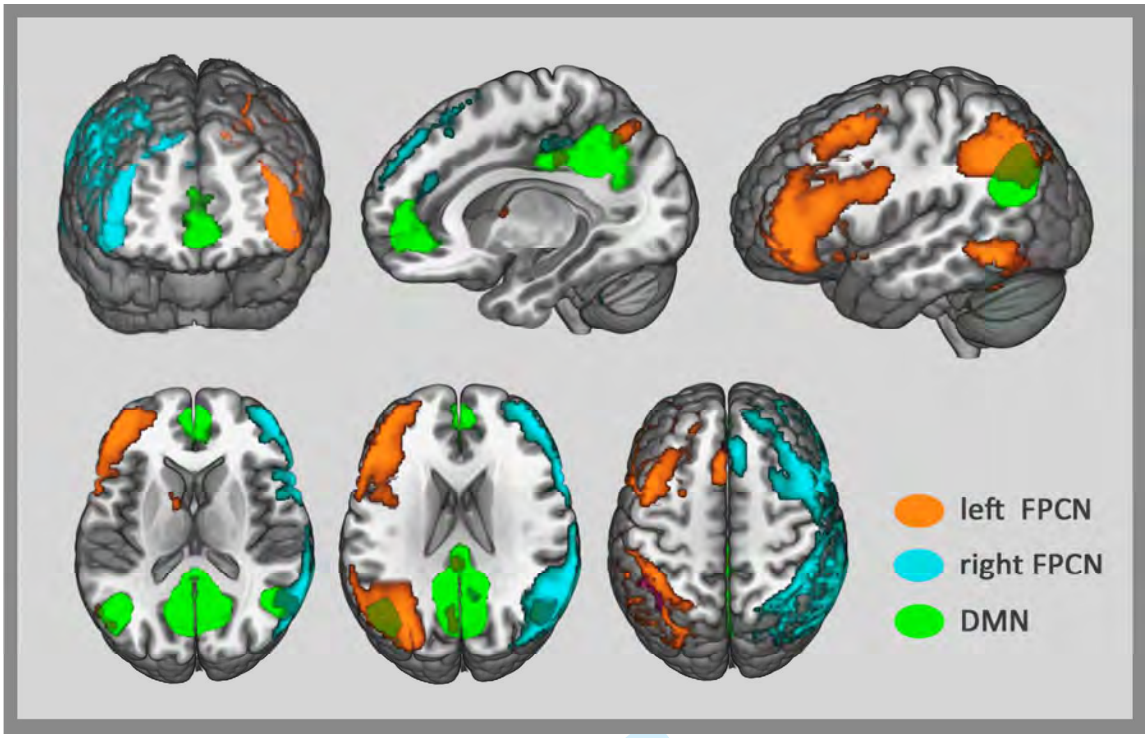
Coverage of all lesions in the frontal lobe.



Warmer colours represent a higher number of lesion overlaps.

Supplementary Fig. 2

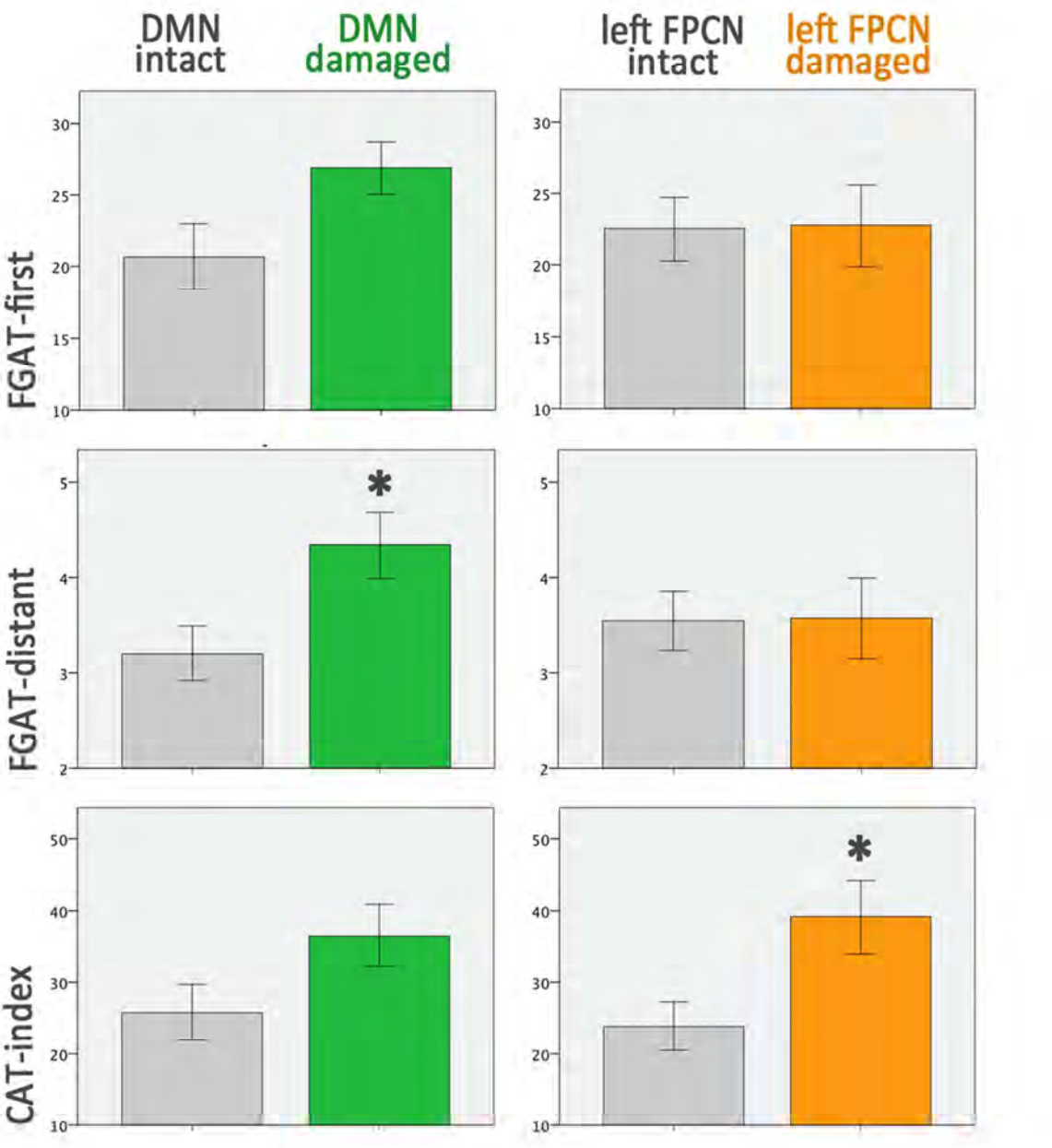
Functional networks described by Smith et al. (2009).



This figure depicts the functional networks described by Smith et al. (2009) as the Fronto-Parietal Control Network (FPCN) represented here in orange for the left hemisphere (network 10) and in blue for the right hemisphere (network 9) and the Default Mode Network (DMN; network 4) in green.

Supplementary Fig. 3

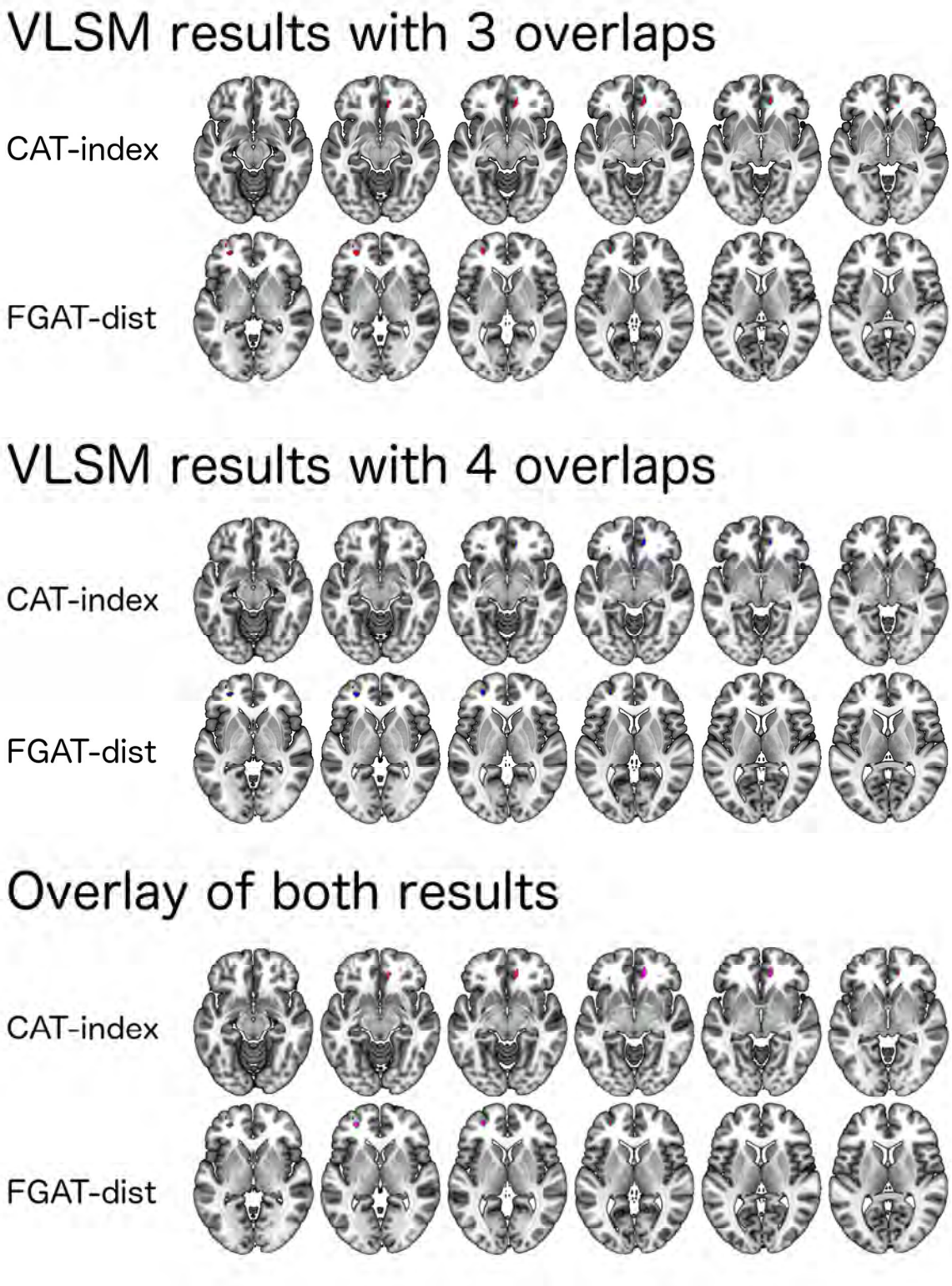
Main scores following damage to distinct functional networks.



This figure depicts the frequency scores on the Y axis at the FGAT-first (first row) and FGAT-distant (second row) conditions, and mean scores on the Y axis on the CAT-index (third row) according to damage to the DMN (spared: gray / damaged: green) or the left FPCN (spared: gray / damaged: orange). *: significant at $P < 0.05$.

Supplementary Fig. 4

Lesion-deficit mapping associated with CAT-index and FGAT-distant performance: comparative results between a 3 and a 4 lesion overlaps threshold.



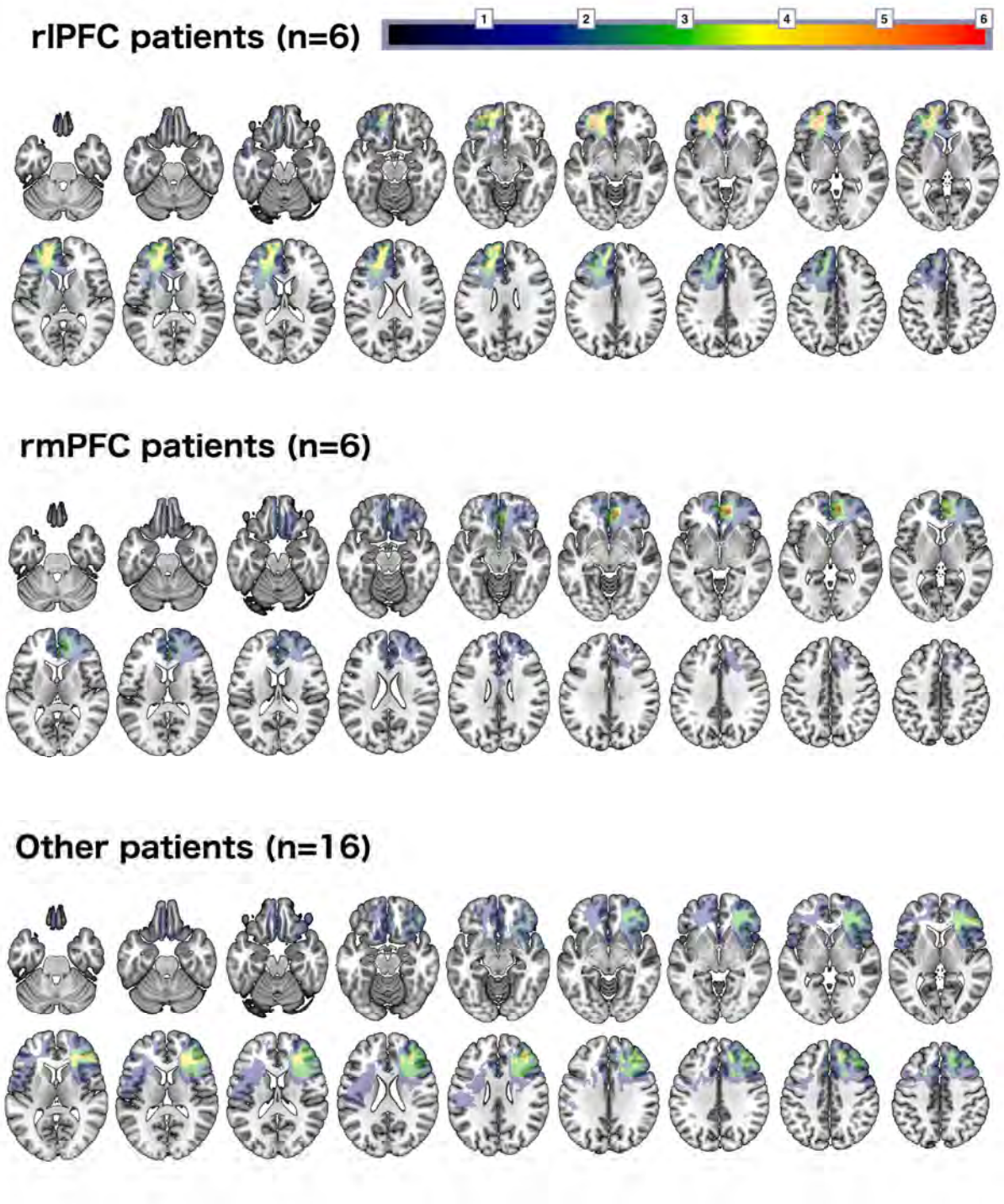
Significant regions are superimposed on axial slices of a brain template in the MNI space. VLSM results using an overlap threshold of 3 lesions are displayed in red, results using an overlap threshold of 4 lesions are shown in blue, and the overlay of both results is displayed in purple. All results were thresholded at $P < 0.05$ with a family-wise errors (FWE) correction for multiple comparisons using permutations. The percentage of prefrontal voxels that satisfied the four overlaps threshold was 22%.

In the left rlPFC region associated with poor CAT-index scores, at an overlap threshold of 4 lesions, Z = 3.540, exceeding the threshold for significance after correction for multiple comparisons using a permutation FWE corrected threshold that was Z > 3.26361632). At an overlap threshold of 3 lesions, Z = 3.615 in the same significant area, exceeding the threshold for significance after correction for multiple comparisons using a permutation FWE corrected threshold that was Z > 3.35279489).

In the right rmPFC region associated with poor FGAT-distant scores, at an overlap threshold of 4 lesions, Z = 3.891, exceeding the threshold for significance after correction for multiple comparisons using a permutation FWE corrected threshold that was Z > 3.32005405). At an overlap threshold of 3 lesions, Z = 3.891 in the same significant area, exceeding the threshold for significance after correction for multiple comparisons using a permutation FWE corrected threshold that was Z > 3.38957906).

Supplementary Fig. 5

Overlap of the lesions for each patient group.



Warmer colours represent a higher number of lesion overlaps.

Supplementary Method 1.

Material and experimental procedure for the Combined Associates Task (CAT)

We built a new verbal task adapted from Mednick's RAT (Mednick, 1962), in which subjects were required to find a word related to three cue words that were presented to them when there was no usual association between these cue words. In the current adaptation of the task, we varied the semantic distance between the cue words and the solution word(s) using association norms. This task has been used in a previous study in healthy subjects (Bendetowicz *et al.*, 2017).

Construction of the material based on measures of semantic distance/strength

Triplets of cue words of variable semantic distance with their solution were created based on free association norms in French, which were available through a published database (Debrenne, 2011) available online (http://dictaverf.nsu.ru/). We used the associative frequency between two words as a measure of semantic distance (or "association strength"). This measure quantifies the proportion of subjects who produced the word B when they were given the word A (for instance, if 334 of 519 participants who were presented the word "woman" responded "man", then the association strength was 334 / 519 * 100 = 64). We selected from the database measures of association strengths obtained from at least 450 adult native French speakers. Associative strength measured from free generation tasks may better capture free word associations (De Deyne *et al.*, 2016) than word co-occurrences in text corpora (such as latent semantic analysis, which has been used before, see Smith *et al.*, 2013; Green *et al.*, 2015) and appeared to be closer to our task condition because participants were required to generate a word based on its associations.

Based on these measures of associative strength, we built 72 trials in the CAT, i.e., 72 triads of unrelated cue words that shared one (or a few) semantic associate(s). We computed the average association strength between the three cue words and the solution word. In cases in which the triad had several possible solution words, the mean association strengths between the cue words and the solution words were summed because each solution word was considered a correct response. The mean association strength of the 72 trials was 9.13 (SD = 7.49), and the median was 7. We classified the trials according to the median of the association strength; 36 trials were classified as "close CAT" trials (associative strength > 7; for instance "rue" (street) – "campagne" (countryside) - "centre" (center), leading to the

solution "ville" (town)), 36 trials were classified as "distant CAT" trials (associative strength < 7; for instance "pont" (bridge) – "social" (social) – "attacher" (to tie), leading to the solution "lien" (link)). The characteristics of the close and distant CAT trials are provided in (Bendetowicz *et al.*, 2017, Table 2). Close and distant CAT trials differed significantly with respect to the mean association strength between the cue words and the solution words, but they did not differ significantly in their mean lexical frequency computed with Lexique 3.80 (http://www.lexique.org; New *et al.*, 2004) as detailed in Bendetowicz et al., 2017.

Words vary in terms of the extent to which they are strongly associated with other words, i.e., associative steepness (Mednick *et al.*, 1964), which may play a role in word generation. We thus controlled the steepness of the cue words in the experiment. A steep word is one for which there is a highly constrained association to one associate, with a much stronger association to this associate than to all the other associates. A flat word is one for which there is a minimally constrained association to other words. The steepness was calculated as the frequency ratio between the second and the first associates of a given word. We defined a word as a steep word when its steepness (the ratio between the associative strengths of its first and second associates) was > 4 and a word as a flat word when steepness was ≤ 3 (Mednick, 1962). The average steepness of cue words in each trial did not differ between close and distant trials (respectively, mean = 2.55, SD = 1.14 and mean = 2.67; SD = 1.76; $U = 627.5$, $P = 0.82$).

Reports of insight

As in Bendetowicz et al. (2017), we assessed the individual tendency to solve the task with insight by collecting subjective reports of the subjective experience of Eureka moments on a trial-by-trial basis, as performed previously (e.g., Kounios & Beeman, 2014). Insight or Eureka is the sudden awareness of the solution to a problem and is accompanied by little or no conscious access to the processing leading up to that solution (Bowden, Jung-Beeman, Fleck, Kounios, 2005; Kounios and Beeman, 2014; Topolinski and Reber, 2010; Weisberg, 2013). This sudden awareness of the solution is often elicited by problem solving tasks such as Mednick's task (Kounios and Beeman, 2014).

Experimental procedure

After the instructions were displayed on a computer screen and explained by the examiner, participants completed 10 practice trials before performing the experimental tasks. In each trial, a set of three unrelated cue words that were arranged in a triangle was displayed on the screen. Participants were asked to give a unique word that was related to all three cue words.

The cue words were displayed on the screen until the participants produced a response, within a time limit of 30 s, and with a visual signal 2 s before the end of the display to warn the participants that time was up. Response times were recorded on the computer by button press, and response words were given orally. The examiner wrote down the subjects' answers.

Five hundred milliseconds after the participant gave his/her answer to each CAT problem, a new screen appeared with the word "Eureka?". Participants were asked to report whether their response came to their mind spontaneously and suddenly or was the direct result of a conscious effortful search. To report their subjective "Eureka" experience, the subjects pressed the keyboard letter "V" if their previous response word had come to mind spontaneously and suddenly without conscious effort. They pressed the keyboard letter "N" otherwise. The participants had 5 seconds to respond. We registered and measured the percentage of "Eureka" reports separately for correctly and incorrectly solved trials (CAT-Eureka).

Trials were separated by two-second inter-trial intervals. The order of trials was randomized between participants, mixing close and distant trials.

Supplementary Method 2

Material and experimental procedure for the Free Generation of Associates Tasks (FGAT)

Participants were asked to generate a word in response of a given cue word according to two distinct conditions. In the "first" condition, the subjects were asked to produce the first word that came to mind. In the "distant" condition, the participants were asked to produce a word that was associated with the cue word in an unusual way. The subjects were instructed to answer with a single word, avoiding phrases, compound words and proper nouns. The same list of 58 words was used in the first and distant conditions.

Construction of the material based on measures of semantic distance/strength

To build the verbal material for the FGAT and to analyze the participants' responses, we used the same published free-association norms as for the CAT (Debrenne, 2011; http://dictaverf.nsu.ru/). We selected words in the database for which associative norms were established based on more than 450 adults who were native French speakers. Ambiguous words such as words corresponding either to an adjective or to a conjugated form of a verb were avoided.

As in the CAT, we explored the steepness of the cue words used. Steepness ranged from 5.58 to 38.00 (mean 12.15) for steep words and from 1.05 to 2.43 (mean 1.58) for flat words. The list of 58 words used in this task included equal proportions of steep and flat words (29 steep words including 11 adjectives, 16 nouns and 2 verbs; and 29 flat words, including 11 adjectives, 16 nouns and 2 verbs). Cue words were reasonably frequent according to mean written frequencies (text- and web-based words computed with Lexique 3.8; www.lexique.org, (New *et al.*, 2004) with a mean lexical frequency of 197 occurrences per millions. Mean lexical frequency did not differ significantly between steep and flat word lists (flat words: 140.98 occurrences per million; steep words: 144.46; $U = 396.0$, $P = 0.70$). Because we were interested in the effect of instruction in the patients, responses to steep and flat cue words were pooled for FGAT-first and FGAT-distant analyses in the current study. Internal reliability was good for both FGAT conditions (Cronbach alpha = 0.911 for FGAT-first and 0.893 for FGAT-distant).

Measures and normative data

Response frequency was calculated in order to estimate the commonness of the words produced by the participants. Response frequency (FGAT-first/distant frequency) was computed for each response as the proportion of healthy subjects who gave this same response based on normative data acquired in a group of 96 healthy subjects (50 females). Mean age = 44.4 years (SD = 14.9), and mean education = 15.3 years (SD = 3.2).

In this sample, there was a significant difference in FGAT frequency between the first and the distant condition for both flat words (FGAT-first flat frequency = 9.91 (2.76); FGAT-distant flat frequency = 3.02 (1.11); Wilcoxon Z = -8.507, $P < 0.001$) and steep words (FGAT-first steep frequency = 35.45 (12.81); FGAT-distant steep frequency = 4.03 (1.75); Wilcoxon Z = -8.507, $P < 0.001$). As the steepness of the cue words had similar effects on response commonness, steep and flat words have been pooled for the analyses.

In addition to FGAT-first/distant frequency, we measured the number of unique responses (FGAT-first/distant unique responses), i.e. the responses provided by a given participant that was not produced by any subject of the normative dataset. We used our sample of normative data rather than the dictaverf database to calculate the commonness of the responses and the number of unique responses because our normative data include both the FGAT-first and FGAT-distant conditions, whereas dictaverf norms were established by asking participants to provide the first word that came to mind (as in our FGAT-first condition) only.

Finally, we also measured the number of typical responses (FGAT-first/distant typical responses). Typical responses corresponded to the most frequent associate for each given cue word based on the association norms (Debrenne, 2011; http://dictaverf.nsu.ru/) obtained in more than 450 participants.

All the responses were screened for general appropriateness. Responses for which there was no intelligible link with the cue, or for which the participant could not explain this link, and responses that were repetition of the cue word were excluded from all analyses. In total, 0.6% of trials in healthy subjects and 0.1% of trials in patients were excluded. In addition, healthy subjects produced no answer in 1.5% of the trials, and patients produced no answer in 5.5% of the trials.

Experimental procedure

After the instructions were displayed on a computer screen and clarified by the examiner, participants performed the experimental tasks as follows. Each trial began with a cue word displayed on a computer screen, and the participant was asked to produce a response word

according to the instruction (first or distant). For each word, participants were given a maximal time of 10 s (FGAT-first) or 20 s (FGAT-distant) to indicate their response by speaking aloud. Responses were written down by the examiner, and RTs were recorded by button press on the keyboard. Once the participant had given his/her response, a blank screen was displayed, and after 2 s, the next trial began. Subjects always performed the first condition before the distant condition. The order of words for both conditions was randomized between subjects.

Supplementary Method 3

Image acquisition, lesion segmentation and spatial normalization.

Patients underwent a high-resolution T1-weighted structural MRI acquisition on a Siemens 3 Tesla (VERIO TIM system) with a 32-channel head coil. A three-dimensional MPRAGE acquisition of 176 axial slices covered the whole brain with a voxel isometric resolution of 1 mm^3 (TE = 2.98 ms, TR = 2300 ms, and flip angle = 9°). Behavioral testing took place on the same day or a few days apart from MRI acquisition for all the participants.

Patient MRIs were preprocessed with SPM8 software (Wellcome Department of Imaging Neuroscience, London, UK), running on Matlab (Mathworks Inc., Natick, USA; www.mathworks.com/matlabcentral). The MRIs were spatially normalized to the Montreal Neurological Institute (MNI) template using the 'unified segmentation' approach combined with lesion masking to limit the impact of a brain lesion on spatial transformations (Crinion *et al.*, 2007; Andersen *et al.*, 2010). This approach appeared to be a good compromise between normalization accuracy and lesion shrinkage (Ripollés *et al.*, 2012). The parameters in SPM were set to the defaults, except that we used a medium regularization (Andersen *et al.*, 2010; Ripollés *et al.*, 2012). Spatially normalized images were resliced to a final voxel size of 1.5 × 1.5 × 1.5 mm3. Normalized MRIs were visually checked and compared with the template to evaluate the normalization accuracy. Signal abnormalities due to the lesions were manually segmented on the normalized MRIs using MRIcron (https://www.nitrc.org/projects/mricron) by trained and experienced neurologists (DB, BG, MLB, EV), who were blind to the performances of the patients at the time of the lesion segmentation. The resulting normalized and segmented lesion volumes were then used in the following analyses.

Supplementary Method 4

We created a prefrontal mask using WFU Pickatlas tool in SPM (http://fmri.wfubmc.edu/software/pickatlas), including all frontal labels of the AAL atlas, and excluding prefrontal gyri and SMA (Frontal_Sup_L, Frontal_Sup_R, Frontal_Sup_Orb_L, Frontal_Sup_Orb_R, Frontal_Mid_L, Frontal_Mid_R, Frontal_Mid_Orb_L, Frontal_Mid_Orb_R, Frontal_Inf_Oper_L, Frontal_Inf_Oper_R, Frontal_Inf_Tri_L, Frontal_Inf_Tri_R, Frontal_Inf_Orb_L, Frontal_Inf_Orb_R, Frontal_Sup_Medial_L, Frontal_Sup_Medial_R, Frontal_Med_Orb_L, Frontal_Med_Orb_R, Cingulum_Ant_L, Cingulum_Ant_R, Rectus_L, Rectus_R). We additionally included in the mask the adjacent white matter. The percent overlap of the lesion map (that included only regions coverage by 3 lesions or more) and the prefrontal mask was calculated using MRIcron.

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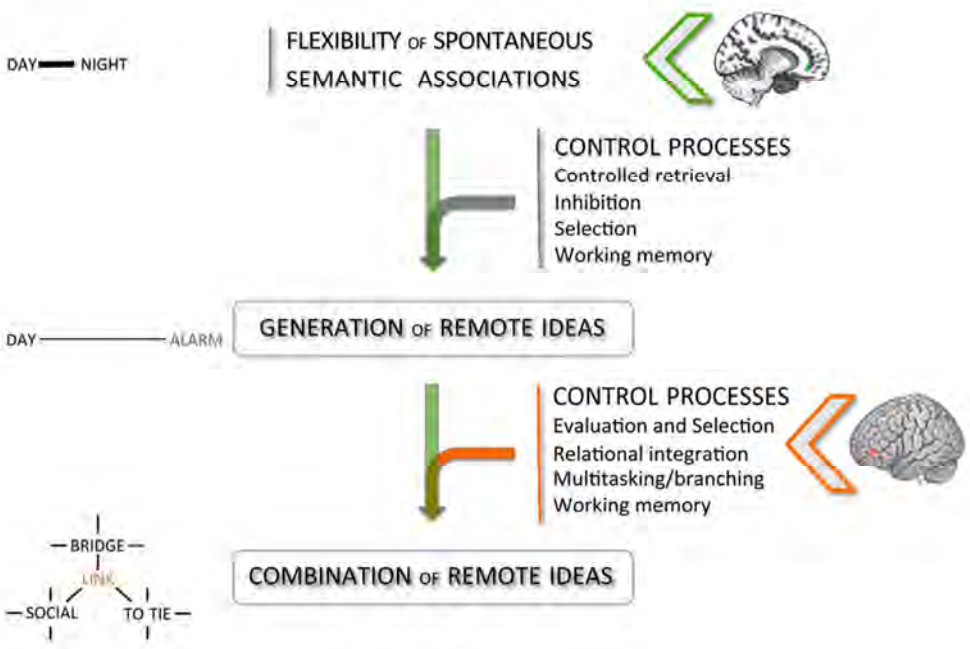
Creative abilities rely on associative and controlled processes likely supported by the default mode network and the frontoparietal network respectively. Bendetowicz et al. show that damage to these networks leads to creativity loss, but affects distinctly both processes. Our findings reveal critical structures that may have distinct roles in creativity.



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