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Reasoning by analogy requires the left frontal pole: lesion-deficit mapping and clinical implications

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Abstract

Analogical reasoning is at the core of the generalization and abstraction processes that enable concept formation and creativity. The impact of neurological diseases on analogical reasoning is poorly known, despite its importance in everyday life and in society. Neuroimaging studies of healthy subjects and the few studies that have been performed on patients have highlighted the importance of the prefrontal cortex in analogical reasoning. However, the critical cerebral bases for analogical reasoning deficits remain elusive. In the current study, we examined analogical reasoning abilities in 27 patients with focal damage in the frontal lobes and performed voxel-based lesion-behaviour mapping and tractography analyses to investigate the structures critical for analogical reasoning. The findings revealed that damage to the left rostrolateral prefrontal region (or some of its long-range connections) specifically impaired the ability to reason by analogies. A short version of the analogy task predicted the existence of a left rostrolateral prefrontal lesion with good accuracy. Experimental manipulations of the analogy tasks suggested that this region plays a role in relational matching or integration. The current lesion approach demonstrated that the left rostrolateral prefrontal region is a critical node in the analogy network. Our results also

suggested that analogy tasks should be translated to clinical practice to refine the neuropsychological assessment of patients with frontal lobe lesions.

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Abbreviations:

AF: arcuate fasciculus; ATR: anterior thalamic radiations; AUC: area under the curve; BA Brodmann area; FAB: frontal assessment battery; FMT: fronto-marginal tract; IFOF: inferior fronto-occipital fasciculus; MFG: middle frontal gyrus; MMSE: mini mental state examination; MNI: montreal neurological institute; ns: non-significant; PFC: prefrontal cortex; rlPFC: rostrolateral prefrontal cortex; ROC: receiver operating characteristic; SD: standard deviation; SFG: superior frontal gyrus; UF: uncinate fasciculus; VLSM: voxel-based lesion- symptom mapping

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Introduction

Using analogies, we can learn abstract concepts and create new associations between distant ideas. Analogies are a powerful tool that allows us to infer general representations from similarities between objects/situations and to transfer this general schema to new cases (Gentner, 1983; Gick and Holyoak, 1983; Gentner *et al.,* 1993; Holyoak and Thagard, 1995; 1997; Gentner and Holyoak, 1997). Hence, analogical reasoning is at the core of generalization and abstraction processes (Holyoak and Thagard, 1995; Thibaut *et al.,* 2010a; Hofstadter and Sander, 2013).

Analogical reasoning combines three key mechanisms: relational processing, similarity processing, and schema inference. Reasoning by analogy depends on the ability to consider, integrate, and compare multiple relationships between components of mental representations (Gentner *et al.,* 1993; Robin and Holyoak, 1995; Gentner and Markman, 1997; Holyoak and Thagard, 1997; Halford *et al.,* 2010). The consideration and integration of multiple relationships (relational reasoning) is also thought to be a key factor for fluid intelligence and to rely on prefrontal functions (Robin and Holyoak, 1995; Duncan *et al.,* 1995; Waltz *et al.*, 1999; Geake and Hansen, 2005; Jung and Haier, 2007). In addition, analogical reasoning depends on the ability to detect similarities between these relational representations (Gentner *et al.,* 1993; Gentner and Medina, 1998; Blanchette and Dunbar, 2000). The comparison and mapping of relational representations composing analogous situations result in the inference of an analogy schema, i.e., a general representation of a pattern of relational similarities (Gick and Holyoak, 1983; Bethell-Fox *et al*., 1984; Gentner *et al.,* 1993; Gentner and Markman, 1997). When a new analogy schema is inferred, new concepts are formed in a flexible manner. Therefore, analogical reasoning allows the study of the relational integration, similarity matching and schema inference processes that are required for abstract thinking and reasoning.

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Despite the importance of these high-level functions in human cognition, deficits in analogical reasoning are rarely assessed in clinical practice, leading to poor understanding of their impacts on patients' daily lives and of their neuroanatomical bases (Ahmed and Miller, 2014). However sparse, previous patient studies have revealed deficits on pictorial and verbal analogy tasks in patient with frontotemporal dementia, suggesting that the prefrontal cortex (PFC) is critical for analogical reasoning (Morrison *et al.*, 2004; Krawczyk *et al.*, 2008). As frontotemporal dementia patients have diffuse prefrontal damage and no voxel-based morphometry analyses have been performed, these studies have not provided evidence of a precise anatomical correlate. In a voxel-based morphometry study of adolescents, traumatic brain injury has been shown to impair performance on a scene analogy task and to alter its correlation with cortical thickness in prefrontal regions (Krawczyk *et al.,* 2010a). The one study that examined focal lesions in adults used a voxel-based lesion symptom mapping (VLSM) approach on (mainly) stroke patients (Schmidt *et al.,* 2012). The results revealed several posterior prefrontal and temporal areas critical for semantic verbal analogies. However, the poor representation of prefrontal damage (n = 17) and of anterior prefrontal lesions in particular in this stroke population limited the conclusions that could be drawn regarding the role of anterior cerebral regions. Among studies that used relational reasoning tasks that are similar to analogy tasks, such as matrix problem tasks (Raven, 1938; Wechsler, 1997), voxel-based lesion studies have also lacked coverage of the rostral PFC region despite larger sample sizes (Gläscher *et al.*, 2009; Baldo *et al.*, 2010), and the conclusions drawn regarding the critical brain regions for these tasks have not always been consistent among studies (Waltz *et al.*, 1999; Tranel *et al.*, 2008; Gläscher *et al.*, 2009; Baldo *et al.*, 2010; Woolgar *et al.*, 2010; Waechter *et al.*, 2013). In related fields that explored abstraction or reasoning, studies in brain-damaged patients have highlighted the critical importance of the left PFC for proverb interpretation (McDonald *et al.,* 2008; Kaiser *et al.,* 2013; Murphy *et al.,*

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2013), conceptualization (Dubois *et al.*, 2000; Delis *et al.*, 2001; Hoffman *et al.*, 2010; Lagarde *et al.*, 2015), and inductive reasoning (Reverberi *et al.*, 2005).

In healthy volunteers, functional imaging studies on analogy have shown the involvement of various prefrontal regions, including the rostrolateral PFC (rlPFC), in addition to parietal and temporal regions (for a review, see Krawczyk, 2012). A variety of analogy tasks have employed verbal, figurative or abstract material that involved semantic (Bunge *et al.,* 2005; Wendelken *et al.*, 2008; Green *et al.* 2010), role-based (Krawcyk *et al.* 2010a), visuospatial, mathematical, or logical relationships (Christoff *et al.,* 2003; Geake and Hansen 2005; Smith *et al.,* 2007; Wartenburger *et al.,* 2009; Cho *et al.,* 2010; Volle *et al.*, 2010; Preusse *et al.,* 2011; Watson *et al.,* 2012). Although domain-oriented or relation-oriented brain regions have been observed (Krawczyk *et al.,* 2011), the rlPFC has been demonstrated to be a domain-general region involved in both semantic and visuospatial analogies (Wendelken *et al.,* 2012) and in both classical analogy and matrix problem solving tasks (Krawczyk *et al.,* 2011). A recent meta-analysis of functional imaging results has shown that the left rlPFC and dorsolateral PFC are the most consistently activated regions across different analogy studies and tasks (Vartanian, 2012). Other approaches such as voxel-based morphometry on healthy volunteers (Aichelburg *et al.,* 2014) and developmental studies of children (Wright *et al.*, 2007; Crone *et al.*, 2009; Thibaut *et al.*, 2010b; Dumontheil, 2014), have also indicated that the left rlPFC is important for various relational reasoning tasks.

In other words, the literature on healthy subjects indicates that the rlPFC, among other regions, plays an important and domain-general role in analogy but the available evidence cannot demonstrate whether it is critical for this process. Patient studies have provided limited conclusions regarding the roles of rostral frontal areas. To the best of our knowledge, no study has examined whether analogical or relational reasoning depends on the integrity of frontal

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lobe connections. Hence, the precise cerebral bases for analogical reasoning deficits and the effect of rostral PFC damage on analogical reasoning abilities remain to be clarified.

In this study, we employed a lesion-behaviour mapping approach in 27 patients with a focal brain lesion in the PFC, to explore the crucial prefrontal regions for analogy and to test whether the left rlPFC is critical. The patients were administered a visuospatial analogy task that has been previously associated with the left rlPFC in healthy subjects (Volle *et al.,* 2010; Aichelburg *et al.,* 2014). The analogy schemas of this task are comparable to those used in previous studies (Gentner and Medina 1998; Krawczyk *et al.*, 2008; Wartenburger *et al.*, 2009; Watson *et al.,* 2012) or in matrix problems. The two analogy conditions used each required relational reasoning and differed only in whether the analogy schema must be inferred. These conditions were compared to a control task that did not require relational processing. Lesion-deficit relationships were explored using a VLSM technique (Bates *et al.*, 2003). In addition, we used a track-wise lesion-deficit analysis (Thiebaut de Schotten *et al.*, 2014; 2015) to explore the impact of tract disconnection on analogical reasoning. Finally, we examined the sensitivity and specificity of these analogy tasks in patients with damaged frontal lobes and estimated the potential value of the task in clinical practice.

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Materials and methods

Participants

Twenty-seven right-handed patients (16 females, mean age of 47.2 years, ranging from 23 to 75 years) who each presented with a single, focal frontal lesion and were seen at the chronic stage (> 2 months) participated in this study. The patients were recruited from the departments of nervous system diseases and neuroradiology at Salpêtrière Hospital, the

neurological unit at Saint-Antoine Hospital and the neuroradiology department at Lariboisière Hospital in Paris. Patients with a history of psychiatric or neurological disease, drug or psychotropic abuse, MRI contraindication or who were not able to understand the task instructions were excluded. All patients were native French speakers. Descriptive and clinical data are reported in Table 1.

The patient performances were compared to those of a normative group of 54 healthy right-handed, French native speaker controls (Supplementary Table 1), who were matched for age and years of formal education and who had no history of psychiatric or neurological disease, drug or psychotropic abuse, or MRI contraindication and no cognitive impairment (Mini Mental State Examination, MMSE ≥ 27/30; Folstein *et al.*, 1975).

The experiment was approved by the local ethics committee; all participants provided written informed consent according to the Declaration of Helsinki and were paid for their participation.

Neuropsychological testing

A battery of neuropsychological tests was administered to all participants (Supplementary method 1). Cognitive status was measured with the MMSE (Folstein *et al.*, 1975). A short assessment of cognitive and behavioural executive functions was performed using the Frontal Assessment Battery (FAB, Dubois *et al.*, 2000), a semantic and lexical fluency task (Cardebat *et al.*, 1990) and the Stroop test (Stroop, 1935). Semantic knowledge was assessed using short French versions of a naming test and a semantic matching test (as described in Merck *et al.*, 2011).

Experimental design

The Analogy and Match (control) tasks of the current study have been used in previous studies in healthy volunteers (Volle *et al.*, 2010; Aichelburg *et al.*, 2014). All of the

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experimental conditions followed the same design and used the same types of stimuli (Fig. 1; Supplementary Method 2). After the instructions were displayed, a first set of stimuli appeared on the left part of the screen (the source set), and two other sets appeared on the right part of the screen (the target sets). The participants were asked to select the target set that matched the source set based on the relationships between the stimuli that composed the sets (Analogy tasks) or based on the similarity of their visual features (Match tasks). The subjects had 11.5 seconds to respond by a button press. The stimuli were letters, numbers or abstract figures, presented in different colours, numbers, sizes or patterns.

Analogy tasks were divided into two conditions: an AnalogyFind and an AnalogyApply condition. In the AnalogyFind condition, the participants had to find the analogy schema by considering the similarities between the structures of each set. The instruction "find analogy" was displayed, and the task required comparing the sets, finding an analogy schema and choosing the target set accordingly (e.g., symmetry of the size of the stimuli). In the AnalogyApply condition, the analogy schema was indicated to the participants by providing them with a verbal term that described it (e.g., "Proportion"). The instruction that contained the verbal description of the schema was displayed on the screen together with the sets; thus, participants still had to consider and compare the multiple relationships between the stimuli, but there was no need to infer or retrieve the schema. Six geometrical or mathematical schemas (proportion, subtraction, addition, mirroring, symmetry and progression) were used and applied to the identity of the stimuli (letters or figures) or to their size, number, brightness, or texture. The features of the stimuli that were not relevant for the analogy schema varied between the source and target, to avoid perceptual matching. For AnalogyApply and AnalogyFind, two types of analogy trials were proposed in the same proportion: intra- and cross-dimensional analogies (Fig. 1).

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In the Match tasks, the source and target sets had to be matched on the basis of six perceptual attributes: colour, quantity, size, texture, figures and letters. As with the Analogy tasks, the Match tasks included two separate conditions, a MatchFind and a MatchApply condition. In the MatchFind condition, the instruction "find match" was displayed, and the participants had to find the perceptual relationship between the source and the correct target set. In the MatchApply condition, the participants were instructed to apply a given matching rule. The instruction that contained a verbal description of the matching rule was displayed on the screen (e.g., "same colours") together with the sets.

All participants understood the instructions and were able to perform the tasks correctly after training. They performed one session of each of the four experimental conditions in the following order: 28 MatchApply trials, 28 MatchFind trials, 48 AnalogyApply trials and 48 AnalogyFind trials. The trials were randomized within each session.

Behavioural Analysis

The accuracy (percentage of correct responses) was measured for each condition. Analogy and Match mean accuracies were calculated by averaging performance on the AnalogyFind and AnalogyApply conditions and on the MatchApply and MatchFind conditions, respectively. Similarly, the Find and Apply performances were calculated by averaging the Find (AnalogyFind and MatchFind) and Apply (AnalogyApply and MatchApply) conditions. We also examined the performance at cross- and intra-dimensional trials for the AnalogyApply and AnalogyFind tasks separately. To assess the possible specificity of the deficits in the Analogy tasks relative to the control task, we also calculated an index (Analogy index = [Analogy mean accuracy – Match mean accuracy] × 100 / mean accuracy in all Analogy and Match tasks averaged). Similarly, we calculated indices to test

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for possible specificity of deficits in the Find condition relative to the Apply condition (Find index = [mean accuracy in Find conditions – mean accuracy in Apply conditions] × 100 / mean accuracy in the average of all conditions), and in the cross- relative to the intra-dimensional analogies (Cross index = [mean accuracy in cross-dimension Analogy trials – mean accuracy in intra-dimension Analogy trials] × 100 / mean accuracy in the average of all analogy conditions).

Statistical analyses were performed using SPSS software (v22.0; LEAD Technologies, Inc.). Between-group differences were analysed using parametric *t*-tests (when the assumption of normality was met) or non-parametric tests otherwise (Mann-Whitney test), using exact *P* values for comparison within our patient group. Correlations between the performances of the patients and age, education, delay or volume of the lesion were analysed using the non-parametric Spearman test (r_s).

Image acquisition and preprocessing

Magnetic resonance Acquisition

Patients and controls underwent the same high-resolution T1-weighted structural MRI acquisition on a Siemens 3 Tesla VERIO TIM system that was equipped with a 32-channel head coil. A three-dimensional MPRAGE dataset that covered the whole brain was acquired for each participant across 176 axial slices with a voxel isometric resolution of 1 mm^3 (TE = 2.98 msec, TR = 2300 msec, and flip angle = 9°). MRI and behavioural testing took place on the same day for most of the participants or a few days apart at most.

MRI spatial normalization

T1-weighted 3D sequences were preprocessed with SPM8 software (Wellcome Department of Imaging Neuroscience, London, UK), which ran on Matlab (Mathworks Inc.,

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Natick, USA; www.mathworks.com/matlabcentral). The MRIs were spatially normalized to the Montreal Neurological Institute (MNI) template. The 'unified segmentation' approach was combined with lesion masking to limit the impact of a brain lesion on the spatial normalization (Crinion *et al.*, 2007; Andersen *et al.*, 2010). This approach has been identified as the best compromise between the normalization accuracy and lesion shrinkage in a recent study (Ripollés *et al.*, 2012). The segmentation parameters were set to the defaults, except for regularization, which was set to medium (Andersen *et al.*, 2010; Ripollés *et al.*, 2012). Spatially normalized images were resliced with a final voxel size of 1.5 × 1.5 × 1.5 mm^3. Each normalized MRI was visually checked and compared with the MNI template to evaluate the normalization accuracy (BG, MLB, DB and EV). No patient had to be excluded due to difficulties with normalization.

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Lesion-behaviour mapping approach

To investigate lesion-deficit relationships, we ran a VLSM analysis (Bates *et al.*, 2003) using NPM software (http://www.mccauslandcenter.sc.edu/mricro/npm/). The preprocessed and normalized MRIs were used for lesion segmentation. Signal abnormalities due to the lesion were manually segmented using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/) by trained neurologists (BG, MLB, and DB) supervised by an experienced neurologist (EV), who were blind to the performances of the patients at the time of the lesion segmentation. The resulting segmented lesion volumes in the MNI space were then introduced in the statistical procedure.

Given the non-normal distribution of the performance and the small sample of the patients, we used the non-parametric Brunner-Munzel test and corrected for multiple comparisons for family-wise errors using permutations, with a significance threshold of $P < 0.05$. Only the voxels that concerned at least three lesions were considered (all of the lesions

together covered 74% of the frontal lobes; overlaps of at least three lesions represented 30% of the frontal lobes). These analyses provided statistical maps for Analogy and Match mean accuracy scores as well as for the Analogy index.

Track-wise lesion-deficit analysis

To explore the impact of tract disconnection on analogical reasoning, we used two track-wise lesion-deficit approaches.

A priori approach.

First, independent of the VLSM results, we used a diffusion-based atlas of frontal lobe connections (Rojkova *et al.*, 2015) combined with Tractotron software as part of the BCB toolkit (http://www.brainconnectivitybehaviour.eu/), to identify the tracts that could be affected by the lesion of each patient. Tractotron automatically computes the overlap of each segmented lesion with the map of the tracts. We mapped the lesion from each patient onto tractography reconstructions of white matter pathways obtained from a group of healthy controls (Rojkova *et al.*, 2015). We quantified the severity of the disconnection by measuring the probability of the tract to be disconnected (Thiebaut de Schotten *et al.* 2014). A tract was considered disconnected when a lesion overlapped with a voxel that belonged to this tract with a probability that was above the chance level (probability > 0.5). We a priori selected several projection tracts that have been associated with Analogy performance according to Aichelburg *et al.* (2014): the long segment of the arcuate fasciculus (AF), the fronto-marginal tract (FMT), the inferior fronto-occipital fasciculus (IFOF), the uncinate fasciculus (UF) and the anterior thalamic radiations (ATRs). Then, we examined the impact of the disconnection of each tract in the left and right hemispheres on analogical reasoning. For each tract of interest, we compared the performance of the patients with and without its disconnection using non-parametric Mann-Whitney tests (with exact P values significant at a $P < 0.05$).

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VLSM-based approach.

Second, based on the VLSM results, we created a map of the tracts connecting the VLSM Analogy region ("VLSM connectome map") and calculated the probability that each lesion intersects this map. We built the VLSM connectome map using Disconnectome map software (Aichelburg *et al.,* 2014; Thiebaut de Schotten *et al.,* 2015) as part of the BCB toolkit (http://www.brainconnectivitybehaviour.eu/). The VLSM region was registered to the tractography of a group of healthy controls (Rojkova *et al.*, 2015) using affine and diffeomorphic deformations. The registered VLSM region was used as a seedpoint to track streamlines passing through the region in a normative dataset. The software creates a probability map of the streamlines intersecting the seed such that the value in each voxel of the map varies based on inter-subject variability. Then, we used Tractotron (Thiebaut de Schotten *et al.,* 2014) (http://www.brainconnectivitybehaviour.eu/), to compute the probability that each lesion intersects the VLSM connectome map. Tractotron also identified the tracts connected to the VLSM region (Rojkova *et al.,* 2015). Among these VLSM connected tracts, we calculated the number of tracts that were disconnected by the lesion of each patient (with probability of greater than 0.5) and examined its correlation with analogy performance.

Sensitivity and specificity of analogy tasks and conditions for clinical use

Finally, we aimed to evaluate the clinical value of the analogy tasks for patients with frontal lobe damage. First, our original tasks in their current form might not be suitable for clinical practice because they take time to perform (between 45 and 50 minutes). Therefore, we ran a new analysis on a subsample of the trials, which was composed of the 28 first AnalogyFind trials (intra- and cross-dimensional) and the 28 MatchFind trials that had been

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administered to each participant. As the order was randomized for each participant, the 28 first Analogy trials were not the same among individuals and were randomly selected. We also checked the reliability of all trials statistically and observed good item reliability (Spearman-Brown coefficient = 0.761). The Apply conditions were discarded because the Find conditions may correspond better to real-life analogies, and they were more strongly impacted by brain lesions. The estimated duration of this subsample of trials did not exceed 15 minutes.

Second, to examine the ability of this shorter version to discriminate among patients, we grouped the patients according to their lesion location, independent of the VLSM results. For analysis of accuracy of the short version, the patients were divided into two a priori-defined groups based on integrity of the left rlPFC. The definition of the group was based on previous literature indicating the importance of the left rlPFC in analogy. Because the rostral PFC is difficult to delineate anatomically, a pragmatic definition was used, as described in Tisserand *et al.* (2002): the rostral prefrontal region corresponds to the most anterior 25 coronal slices (2.5 cm), $y > 44$ in the MNI coordinates. Within this rostral prefrontal region, we selected its left lateral part (defining the 'left rlPFC region') by selecting MNI x coordinates that were lower than -25. Seven patients had a lesion that affected this anatomically defined rlPFC region and were pooled in the 'damaged left rlPFC' group (indicated in Table 1). Their performances were compared to patients who had an intact left rlPFC ('intact left rlPFC' group).

We then examined the sensitivity and specificity of this shorter subtask to discriminate brain lesions, by building Receiver Operating Characteristic curves (ROC curves) for each score. These ROC curves show the trade-off between the sensitivity and specificity, and the area under the curve (AUC) estimates the accuracy of the task for predicting the left rostrolateral damage in patients who had frontal lesions. Based on the obtained predictive

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value of the Analogy and index scores and on the normative scores of controls, we grouped the patients according to the presence or absence of a deficit in analogical reasoning (indicated in Table 1) and compared their cognitive profiles and lesion locations.

Results

Behavioural results

The patients exhibited significantly poorer performances compared with the controls on the FAB, fluency tasks, and MMSE, and they showed a greater interference effect on the Stroop test, but their semantic knowledge was preserved (Supplementary Table 1 and Supplementary Fig. 1).

The patients performed significantly more poorly than the healthy participants in terms of both the Analogy conditions separately and the Analogy mean accuracy score. They had lower Match mean accuracy scores, whereas their accuracy in each Match condition separately did not differ from that of the controls. The Analogy index was significantly higher in the patient group, which suggests that their deficit was larger in the Analogy than the Match tasks. The patients scored lower than the healthy subjects in the Find and Apply conditions, but not in the Find index, which suggests that they were equally impaired in the Apply and Find conditions.

Although age, lesion volume and lesion delay, and in some cases education, can be confounding factors in VLSM analysis, there was no significant correlation between Analogy mean accuracy score and age ($r_s = -0.276$, ns), education ($r_s = 0.336$, ns), lesion volume ($r_s = -0.314$, ns), or lesion delay ($r_s = -0.201$, ns), which have not been covaried out.

VLSM Results

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The statistical map of the Analogy mean accuracy score (Fig. 2) showed that a deficit in the Analogy tasks was associated with a left rostral prefrontal area (MNI coordinates centred on -31, 51, -3; z = 3.48; volume = 0.33 cc) that encompassed BA 47/10 and was located at the rostral junction between the superior and middle frontal gyrus (SFG and MFG), extending into *pars triangularis*. A smaller cluster was located posteriorly, centred on coordinates -34, 41, 3, and another in the orbitofrontal cortex, BA 47 and 11, centred on coordinates -30, 41, -10. These clusters are gathered under the term 'the VLSM Analogy region' in the further analyses below.

Table 2 shows that the patients who contributed to the 'VLSM Analogy region' (n = 5) did not differ from the other patients in terms of their age, education, lesion volume, delay between lesion and inclusion, and general neuropsychological testing, except for the Stroop test, in which they had a stronger interference effect. The patients contributing to the 'VLSM Analogy region' had lesions caused by various mechanisms, including haemorrhage (P02 and P29), tumour excision (P04 and P08) or epilepsy surgery (P22), as indicated in Table 1.

Patients with a lesion in the 'VLSM Analogy region' showed significantly greater impairment than the other patients on the Analogy tasks but not on the Match tasks, as shown by a significant between-group difference in the Analogy index (Fig. 3 and Table 2). There was no between-group difference in the Find index or the Cross index. In other words, the 'VLSM Analogy' patients were not differentially affected compared with the other patients by the need to infer the analogy schema (no significant difference in the Find index) or to transfer the schema to different dimensions in the source and target (no significant difference in the Cross index). For subsequent analyses, intra- and cross-dimensional trials, as well as Apply and Find analogy trials, were pooled.

We also ran VLSM maps for the mean Match score and found no significant results.

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The statistical map for the Analogy Index (Fig. 2) revealed a region that was very close to the 'VLSM Analogy region' in the MFG and *pars triangularis*, which encompassed BA 10, 47, 45 and 46 and was centred on the MNI coordinates -35, 48, and 9 (volume of 1.57 cc). Although the VLSM Analogy and VLSM Index regions did not fully overlap, they both included BA10 and 47 in the left rlPFC, indicating that the left rlPFC was specifically critical to Analogy relative to Match.

Track-wise Lesion-Deficit approach

A priori approach

Several tract disconnections had impacts on analogical reasoning abilities. Table 3 shows that disconnections of the left IFOF, UF and FMT were associated with a greater deficit in Analogy tasks (Analogy mean accuracy score and Analogy index). Disconnection of the left ATR was associated with a deficit in the Analogy tasks, but no significant association was observed with the Analogy index. Age, education, lesion delay and lesion volume did not significantly differ between the 'Disconnected' and 'Intact' groups for these four analogy-related tracts, except that the patients with a UF disconnection had an increased age. Disconnection of the left AF was not associated with a significant deficit, perhaps because it was disconnected in only five patients. None of the selected tracts in the right hemisphere was associated with a deficit in an Analogy or Match tasks when disrupted.

Both the VLSM and disconnection approaches show that left-brain lesions were associated with analogical difficulties. Note that none of the descriptive, clinical or neuropsychological data significantly differed between the right-brain-damaged (n = 9) and left-brain-damaged patients (n = 14) (Supplementary Table 2).

VLSM-based approach

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In a second approach, we built the VLSM connectome map composed of the tracts connected to the VLSM Analogy region. This map is shown in Supplementary Fig. 2. For each patient, the probability of disconnection of the VLSM connectome map and the number of disconnected tracts among the VLSM connected tracts are provided in Supplementary Table 3. The probability of disconnection of the VLSM connectome map was significantly correlated with the Analogy mean accuracy score (r_s = - 0.511; P = 0.006) and with the Analogy Index (r_s = –0.471; P = 0.013). This result indicates that a lesion that disconnected the 'VLSM Analogy region' affected analogical reasoning. The correlations of the probability of disconnection of the VLSM connectome map with age (r_s = 0.262), education (r_s = – 0.201) and lesion volume (r_s = 0.366) were not significant.

Tracts connected to the VLSM Analogy region included the left ATR, FMT, IFOF, UF, orbitopolar tract, superior longitudinal fasciculus (branch 3), fronto-pontine projections, and frontostriatal fasciculus. Among these tracts, we observed significant correlations between the number of disconnected tracts per patient and the Analogy mean accuracy score (r_s = - 0.553; P = 0.003) as well as the Analogy Index (r_s = - 0.416; P = 0.031). Correlations with age (r_s = 0.334), education (r_s = - 0.131) and lesion volume (r_s = 0.024) were not significant. Among all other tracts (tracts not connected to the VLSM analogy region), the Analogy mean accuracy score and Analogy index were not correlated with the number of disconnected tracts per patient (r_s = 0.126 and 0.122, respectively; ns), but lesion volume was correlated (r_s = 0.693; P < 0.001). These findings indicate that analogical reasoning depends on connectivity of the VLSM region independent of lesion size.

Value of Analogy tasks in clinical practice

To further explore the value of our analogy task in clinical practice, we analysed a subsample of the original trials. Patients in the 'damaged left rlPFC' group (with left rlPFC anatomically defined, n = 7) had poorer performances than those in the 'intact left rlPFC'

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group (n = 20) in the AnalogyFind-short version condition but not in the MatchFind-short version condition, and their Analogy index-short version was significantly greater (Supplementary Table 4).

We explored the discriminative value of the short version of the analogy tasks with regard to brain damage location (damaged versus intact left rlPFC) using ROC curves (Supplementary Fig. 3). The AUCs showed that the accuracies of the AnalogyFind-short version performance (AUC = 0.925; P = 0.001) and of the Analogy index-short version (AUC = 0.954; P < 0.001) were very good, but that the MatchFind-short version discriminated among the patients poorly (AUC = 0.707; P = 0.109).

Examination of the coordinate points of the ROC curves showed that an AnalogyFind-short version score of below 65.3% (which corresponds to the mean performance of the controls minus 1.5 SD) had a sensitivity of 85.7% and a specificity of between 85 and 90%. An Analogy index-short version that was lower than – 33% (absolute value > 33) had a sensitivity of 85.7% and a specificity of between 90 and 95%. The Analogy index-short version was as sensitive as the AnalogyFind-short version when discriminating the patients, and it had a slightly better specificity. Thus, an Analogy index-short version score that exceeded 1.5 SD from the mean score of the healthy controls (< – 33%) was used as a cut-off to define an analogical reasoning impairment.

To further characterize the value of such a cut-off in brain-damaged patients, we analysed the cognitive profile and visualized the lesion location of the patients as a function of their deficit in analogical reasoning.

Table 4 shows that the two groups did not differ significantly in age, education, lesion volume, mean lesion-testing delay or neuropsychological scores, especially for those tasks that tap into executive functions (see also Table 1). This finding suggests that other cognitive deficits cannot explain the analogy difficulties. Fig. 4 shows that the lesions of the patients

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with impaired analogical reasoning overlapped mainly in the left rlPFC region, whereas the lesions of the patients with preserved analogical reasoning overlapped in the right PFC.

In summary, the short version of the tasks was sufficiently sensitive to confirm the critical role of the left rlPFC in analogical reasoning, with a high accuracy of the Analogy index in distinguishing the patients with a left rlPFC lesion.

Discussion

The current study focused on the impacts of prefrontal lesions on analogical reasoning. The results obtained using three distinct approaches (VLSM, disconnection, and ROC analyses) converge to show the critical role of the left rostral prefrontal region in analogical reasoning. Two new findings emerge from this work. First, analogical reasoning specifically depends on the integrity of the left rlPFC and/or on the integrity of some of its long-range connections. Second, our analogy task very accurately predicts a left rlPFC lesion and could be used as a new tool to assess brain-damaged patients. These findings have important clinical implications because analogical reasoning and the more general functions of the rostral part of the PFC are poorly assessed in clinical practice.

Analogy and the integrity of the prefrontal cortex and/or its connections

Few data are available regarding analogical reasoning abilities in patients with brain damage. Following the two studies that explored neurological patients with diffuse frontal damage (Morrison *et al.*, 2004; Krawczyk *et al.*, 2008), the current VLSM analysis specifies which area in the PFC is critical for analogical reasoning. This critical area is located in the rlPFC, encompasses BA 10 and 47 and is left lateralized (Fig. 2). A lesion of this region is not associated with a deficit in the perceptual matching condition, which suggests that analogical reasoning is relatively specifically impaired when this region is damaged (Table 2 and Fig. 3). As illustrated in Supplementary Fig. 4, this result converges with the conclusions drawn from

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other approaches, such as functional imaging (Volle, *et al.*, 2010; and for reviews Krawczyk, 2012; Vartanian 2012) and morphometry (Aichelburg *et al.*, 2014). The left rlPFC has been observed in functional imaging studies using different analogy tasks that involved distinct types of relationships in the semantic or visuospatial domains, which suggests a domain-general role of the left rlPFC in analogies. However, the precise role of this rlPFC region in analogy, and in cognition in general, is not clearly understood. Previous studies have suggested that this rlPFC region is involved in relational integration (Christoff *et al.*, 2001; Kroger *et al.*, 2002; Ruff *et al.*, 2003; Ramnani and Owen, 2004; Krawczyk *et al.*, 2011), abstraction (Christoff *et al.*, 2009), and the mapping of similarities (Bunge *et al.*, 2005; Garcin *et al.*, 2012). Our task manipulation did not provide evidence of a significant difference that would have suggested a role in inference processes (Find *vs.* Apply) or in remote mapping that allows for abstract generalization (Cross- *vs.* Intra-dimensional analogy), although there is evidence from other studies that the left PFC is important for rule induction (Reverberi *et al.*, 2005) and for distant analogies (Green *et al.*, 2010). However, in patients with left rlPFC damage, the deficit was deeper for inferences based on cross-dimensional mapping (Table 2; Fig. 3). Thus, it remains possible that these differences exist but were missed because of a lack of sufficient statistical power or due to insufficient lesion overlap.

A left dominance of PFC for analogical reasoning was previously highlighted in functional imaging studies (Bunge *et al.*, 2009; Vartanian, 2012) and in one repetitive transcranial magnetic stimulation study (Boroojerdi *et al.*, 2001). However, the lateralization of rlPFC functions is not understood. The role of language in analogies could be at play, but it cannot entirely explain a left lateralization because tasks that used non-verbal analogies also recruited the left rlPFC (Wharton *et al.*, 2000; Christoff *et al.*, 2003; Bunge *et al.*, 2009; Hampshire *et al.*, 2011; Watson and Chatterjee, 2012; Wendelken *et al.*, 2012), and analogical reasoning difficulties are not associated with reduced fluencies in our patients.

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VLSM analysis did not identify other critical prefrontal areas for analogies, although previous functional imaging studies have shown that several prefrontal regions are involved in analogical reasoning (Christoff *et al.*, 2001; Bunge *et al.*, 2005; Geake and Hansen, 2005; Green *et al.*, 2006; Cho *et al.*, 2007; Wendelken *et al.*, 2008; Geake and Hansen, 2010; Krawczyk, *et al.*, 2010b; 2011; Volle, *et al.*, 2010; Hampshire *et al.*, 2011; Preusse *et al.*, 2011; Green *et al.*, 2012; Krawczyk, 2012; Wendelken *et al.*, 2012), as well as temporal and parietal regions. Within the PFC, it is possible that the other prefrontal regions that support analogical reasoning are less lateralized, which allows for the contralateral cortex to compensate for this function. However, we cannot exclude the possibility that the analyses missed some other critical prefrontal region because of the lack of statistical power achieved for some of the regions and because only partial coverage of the frontal lobes was obtained. It is likely that the left rlPFC operates via interaction with more posterior regions in the prefrontal, parietal and temporal lobes (Aichelburg *et al.*, 2014; Cocchi *et al.*, 2014; Rojkova *et al.*, 2015). Because we examined only patients with prefrontal brain lesions, no conclusion could be made on the critical roles of the parietal and temporal lobes. Nevertheless, our track-wise lesion-deficit approach provided some clues about the roles of the interactions of the left rlPFC with other brain regions for analogy performance.

We found that disconnection of the left IFOF, UF, FMT, or ATR was associated with a deficit in Analogy tasks (Table 3). These results are consistent with a previous tractography study in healthy subjects (Aichelburg *et al.*, 2014) and confirm the importance of the left hemisphere for analogical reasoning. Here, anatomical connections between the temporal cortices (via the UF), the occipital cortex (via the IFOF), and subcortical structures via the ATRs appear to play a role in analogical reasoning. The VLSM-based approach further showed that an analogical reasoning impairment was associated with a disconnection of the

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VLSM Analogy region. Owing to these connections, information can converge within the left rlPFC, coming from distinct domains or networks (Sakai *et al*., 2003; Parkin *et al.,* 2015)

Recent resting-state studies have emphasized the importance of functional networks for high-level cognitive functions and that the disruption of these networks could better explain a deficit in high-level cognition than lesion location *per se* (Woolgar *et al.*, 2010; Gratton *et al.*, 2012; Warren *et al.*, 2014; Corbetta *et al.*, 2015). In this context, the result that a very circumscribed lesion site is critical for analogical reasoning is puzzling. This lesion site may be critical because damage to this area cannot be compensated for and/or because several tracts that converge at this site must be conjointly damaged to provoke a deficit, as suggested by the correlation between analogy performance and the number of tracts connected to this region that were affected by the lesions. This latter interpretation would match the cortical disconnection mechanism that was previously hypothesized by Norman Geschwind (1965). Overall, these results suggest that the left rlPFC region is a functional "hub" or an essential relay station in the analogy network. This interpretation argues for the role of this region in integrating information of different natures or domains.

Clinical application of the study: a new assessment tool

Although recent cognitive theories based on functional imaging place the rostral PFC at the top of a frontal hierarchical functioning model that subserves reasoning, problem solving, behavioural adaptation and abstraction (Badre and D'Esposito, 2007; Koechlin and Summerfield, 2007; Badre, 2008; Christoff *et al*., 2009; Krawczyk et al., 2011), functions of the rostral PFC are poorly assessed in clinical practice. Only recently has Burgess and Shallice's work on multitasking (Shallice and Burgess, 1991) generated specific tasks for physicians (Burgess *et al.*, 2006; 2009). Existing neuropsychological tools offer very few tests of abstract thinking or reasoning, and the critical brain networks for these tests are not well understood, as mentioned in the introduction. The conceptual framework of analogical

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reasoning provides cognitive tasks that tap into abstract thinking and relational reasoning abilities, and the cerebral networks associated with these tasks have begun to be clarified. Hence, patients could benefit from the transfer of analogical reasoning tasks to clinical practice. In this study, we simulated a short version of our analogy task that could be transferred to clinical practice and showed that it had very good sensitivity and specificity for predicting left rlPFC injury, which demonstrates that even a small set of analogy trials is valuable for discriminating among different types of patient damage (Supplementary Fig. 3). The Analogy index appeared to be the most specific measure for analogical reasoning deficits.

Impairment in our Analogy tasks was not associated with global executive dysfunction, which suggests that analogical reasoning is a cognitive ability that is not entirely captured by classical executive neuropsychological tests (Table 4). Our results rather support a functional specialization within the PFC, with a distinct role of the rostral PFC compared with the more posterior areas. Previous studies have highlighted the role of inhibition abilities and interference control for analogical reasoning (Morrison *et al.*, 2004; Krawczyk *et al.*, 2008; Bugaiska and Thibaut, 2015). These studies suggest the possibility that analogy deficit in patients with left rlPFC lesion may be due to poor inhibition abilities. Although our VLSM analysis cannot rule out this explanation, other parts of our findings do not favour this hypothesis because patients with impaired analogy scores did not have more interference sensitivity than patients with preserved analogy scores (Table 4). In addition, response inhibition is usually associated with right or medial frontal regions (Stuss *et al.*, 2001; van Veen and Carter, 2005; Volle *et al.*, 2012; Tsuchida and Fellows, 2013; Aron *et al.*, 2014; Hornberger and Bertoux, 2015; Robinson *et al.*, 2015).

Finally, patients with frontal lesions of different aetiologies have been included in this study, which is a limitation because different pathologies affect the brain differently with distinct time courses and mechanisms of plasticity. However, a recent study has demonstrated

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that frontal lesions of different vascular and tumour aetiologies have similar effects on executive testing and fluid reasoning (Cipolotti *et al.,* 2015). This finding supports the idea that the pooling of lesions with various physiopathological mechanisms in the same analysis is a valid methodological approach to exploring the organization of frontal functions. This approach has been used previously (Volle *et al.,* 2008; 2012; Tsuchida and Fellows, 2013; Azuar *et al.,* 2014), including lesions caused by epilepsy surgery (Tranel *et al.,* 2008; Gläscher *et al.,* 2009; Chapados and Petrides, 2013). The pooling of lesions with different physiopathological mechanisms allowed us to more completely cover the possible lesion locations in the PFC, including the rostral part, which is rarely affected by ischaemic strokes. Furthermore, this approach could mitigate statistical and spatial biases due to stroke locations (Nachev *et al*., 2008; Volle *et al*., 2013; Mah *et al.*, 2014). In this context, our findings suggest that assessing analogical reasoning in brain-damaged patients has a clinical value that is independent of the lesion aetiology.

Overall, the short version of our analogy task could enrich the classical neuropsychological toolbox for the assessment of high-level cognitive functions that depend on the rostral PFC. The ecological validity of this test in real-world problem solving remains to be demonstrated. Hence, the short version of the Analogy test will be validated in an independent and larger sample of patients with more homogeneous lesions and in a group of controls matched for age and education. We will examine correlations to other relational reasoning or problem solving tasks to further improve the value of the test as a tool for the evaluation of analogical reasoning abilities in clinical practice.

Conclusions

Analogical reasoning plays a significant role in inferring general representations from similarities, which in turn can be applicable to solving new problems. The current lesion study has demonstrated for the first time, using three distinct approaches, that the left rlPFC (along

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with its long-range anatomical connections) is specifically critical for analogical reasoning and that a left rlPFC lesion could impair the relational integration and matching processes that are involved in abstract thinking. Despite a relatively small sample size examined in this study, these results converge clearly with existing neuroimaging findings on analogy. Furthermore, our study provides a sensitive and specific new neuropsychological test that can be transferred to everyday clinical practice, for the assessment of analogical reasoning in patients. These findings could be useful to clinicians by informing them of the expected consequences of rostral prefrontal damage on high-level cognitive functions and proposing a tool for their assessment.

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Supplementary material

Supplementary material is available.

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Figure legends

Fig. 1: Examples of Intra- and Cross-dimensional Analogy and Match trials. In each example, for clarity, source sets are framed in white, and target sets are framed in red, although in the real tasks, the sets were all framed in light grey when they were displayed to the participants. The left column displays an intra-dimensional analogy, and the middle column displays a cross-dimensional analogy, using the same analogy schema 'symmetry'. In the intra-dimensional analogy, the symmetry is on the same dimension in the source and target sets. The correct answer in the top left example (AnalogyFind) is the top target, in which there is symmetry of the letter identity in both the target and source sets. The correct answer in the bottom left example (AnalogyApply) is the bottom target, in which there is symmetry of the colour in both the target and source sets. In cross-dimensional analogy, the symmetry concerns different dimensions in the source and target sets. The correct answer in the top middle example (AnalogyFind) is the bottom target, in which there is symmetry of size, whereas the source set has symmetry of letter identity. In the bottom middle example (AnalogyApply), the correct answer is the top target. The right column displays a Match trial. Correct answers are the bottom target for the top trial and the top target for the bottom trial. For each of these tasks, the participants performed Find and Apply conditions. The upper row presents Find trials, in which the abstract similarity (in the Analogy task) or the feature similarity (in the Match task) was not given to the participant. The bottom row presents Apply trials, in which the abstract similarity or feature similarity was given in the instruction. Three distinct analogy schemas were used in the AnalogyFind condition, and three other schemas were used in the AnalogyApply condition. The three matching rules used in the MatchFind condition were distinct from the three rules used in the MatchApply condition.

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Fig. 2: Overlaps of patient lesions and statistical VLSM maps obtained for the Analogy mean accuracy and Analogy Index scores. The VLSM maps are superimposed on a normalised T1 MRI from a single subject in MNI space. Statistical maps were generated using the Brunner-Munzel test. Maps were thresholded at a $P < 0.05$ and corrected for multiple comparisons (family-wise error correction by permutations).

Fig. 3: Analogy performance of patients with a lesion involving the 'VLSM Analogy region' compared to those with a lesion that spares this region and to healthy subjects. The mean accuracy (in %) and SD (error bars) under each experimental condition are displayed for patients with a lesion involving the VLSM Analogy region associated with a deficit in Analogy mean accuracy scores (in dark grey), for patients with a lesion that spares this region (in light grey) and for healthy subjects (in very light grey). The performance on the Analogy tasks (but not on the Match tasks) differed significantly between the two patient groups. *: Significant difference at a $P < 0.05$ between patients with a lesion involving the 'VLSM Analogy region' compared to those with a lesion that spares this region.

Fig. 4: Overlays of lesions from patients with specific impairment in analogical reasoning and from patients with normal performance. Patients with impaired analogical reasoning were defined by an Analogy index < -1.5 SD of the mean score of the healthy subjects ($n = 7$ patients) in the short version of the tasks. Analogical reasoning was considered 'intact' when the Analogy index was within 1.5 SD of the mean score of the healthy subjects ($n = 20$ patients). The colour code is represented on the upper right-hand side, and it ranges from white ($n = 1$) to red ($n = 6$), indicating maximum overlap. The axial slices range from Z = -12 to Z = 23 in the MNI.

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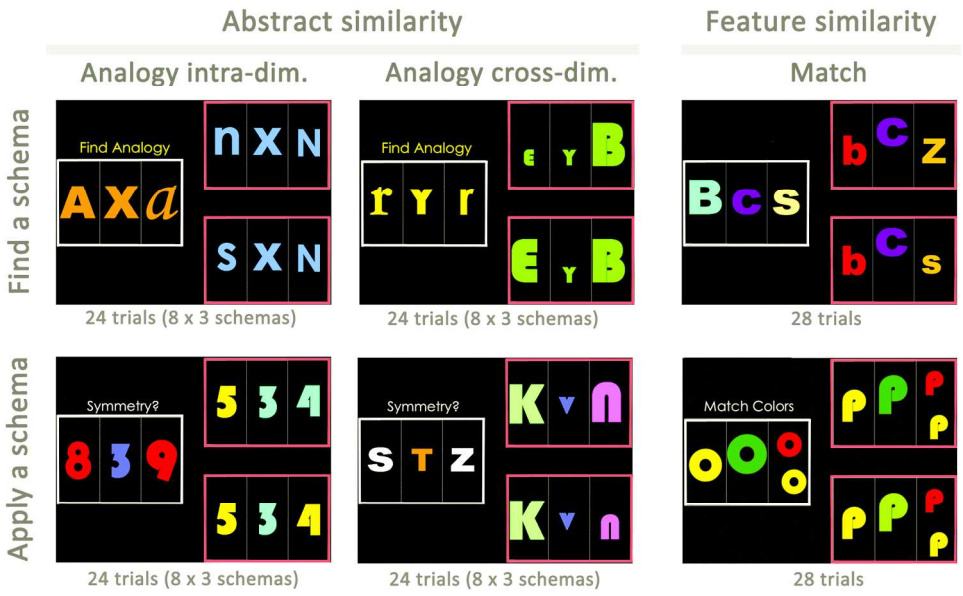

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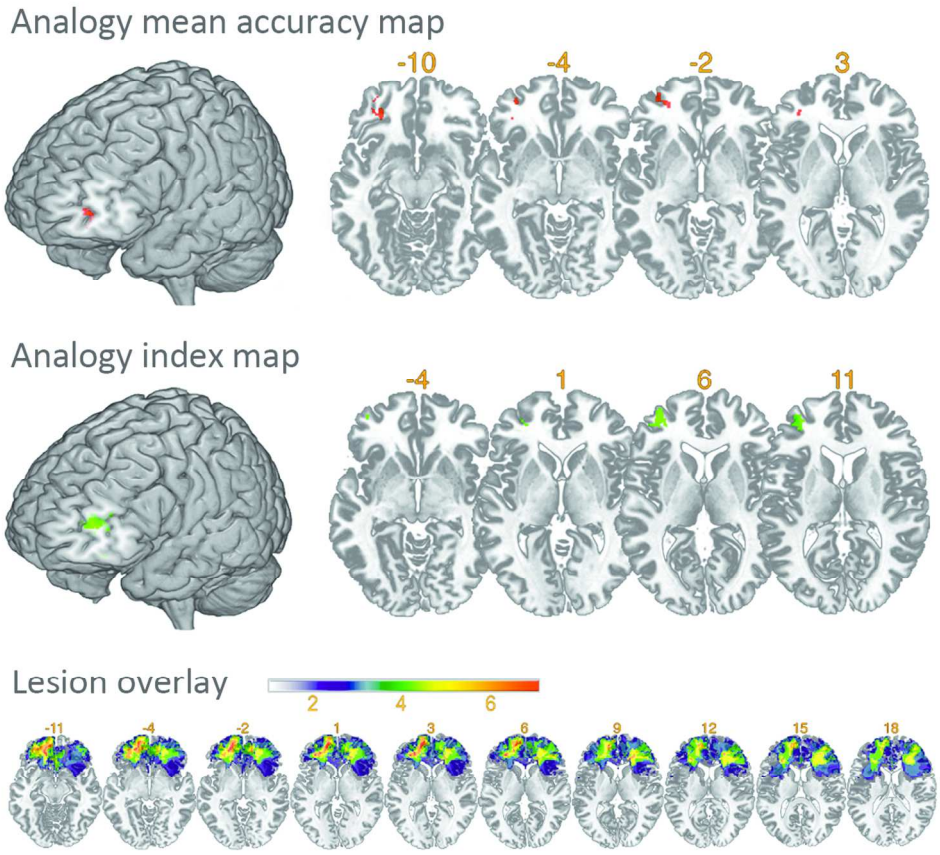

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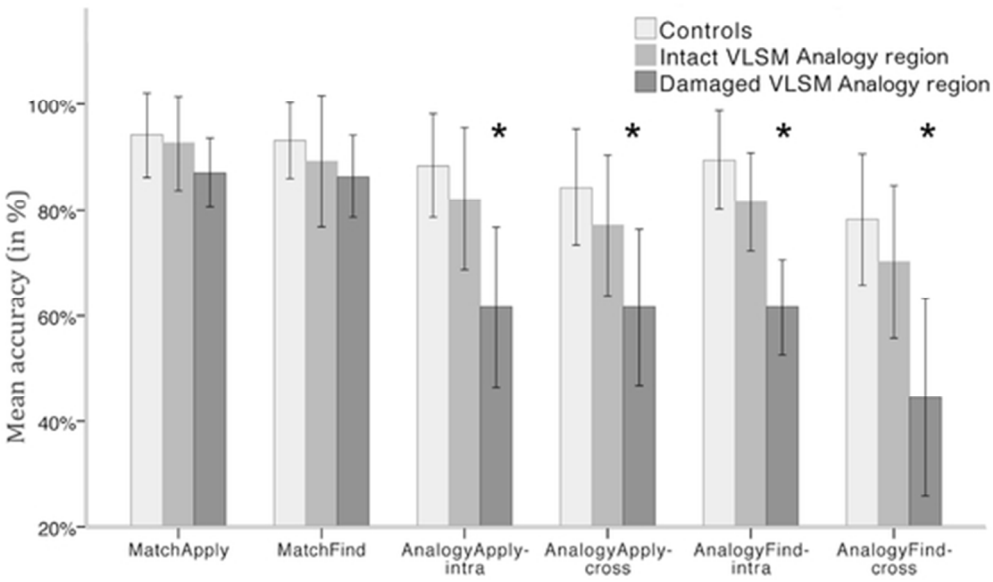

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47x27mm (300 x 300 DPI)

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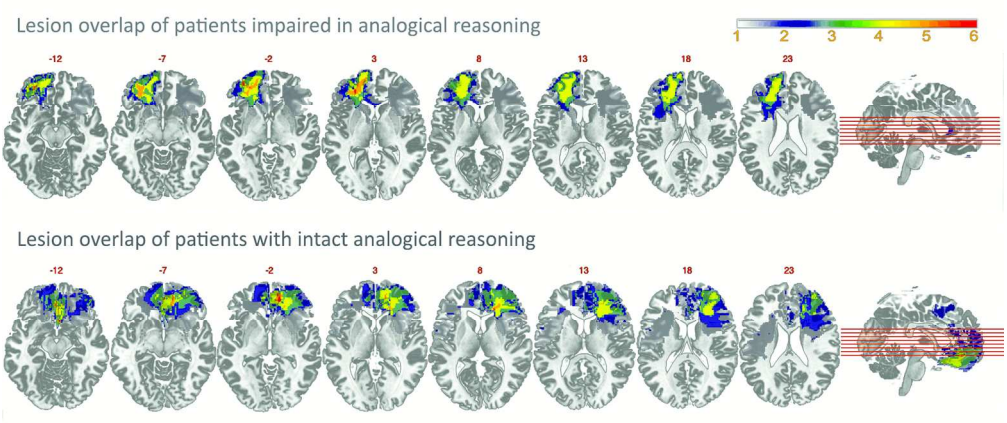

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Table 1: Clinical, descriptive information, and performance for the 27 patients included in the study. Patients who participated in the VLSM Analogy region are indicated in the "VLSM" column. Patients impaired in the short version of the task (Analogy index) are indicated in the "Deficit- short task" column.

Patient	Age (years)	Gender	Education (years)	Aetiology	Lesion side and location	Interval (months)	Lesion volume (cc)	VLSM	Deficit - Short task
P01	56	F	17	Ischemic stroke	R - Semioval center	7	0.27		
P02	55	M	19	Hemorrhage S	L - rostral PFC / VMPFC*	76	38.87	+	+
P03	46	F	17	Ischemic stroke	L - posterior MFG	126	21.22		
P04	50	F	11	Low-grade glioma (excision)	L - rostral PFC+ / VMPFC*	137	150.85	+	+
P05	64	M	14	Ischemic stroke	R - IFG and MFG	121	76.63		+
P06	32	F	16	Epilepsy surgery	R - posterior SFG	133	22.43		
P08	70	F	5	Meningioma (excision)	L - rostral PFC+*	85	55.60	+	+
P09	47	M	11	Hemorrhage RA	R - Cingulate / VMPFC	115	13.79		
P10	62	F	13	Hemorrhage RA	B - Cingulate / VMPFC	14	44.12		

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P11	41	M	16	Epilepsy surgery	R – IFG / MFG / posterior SFG	29	67.13	
P12	46	M	12	Hemorrhage RA	B - Cingulate / VMPFC	51	9.29	
P13	67	M	15	Ischemic stroke	L - anterior IFG	133	4.71	
P14	49	M	9	Hemorrhage RA	B - Cingulate / VMPFC	19	23.17	
P15	36	F	14	Epilepsy surgery	R - rostral PFC / VMPFC	82	49.67	
P16	40	F	22	Hemorrhage S	L - rostral PFC*	56	27.59	+
P17	40	M	14	Hemorrhage RA	B - rostral PFC / VMPFC	7	26.71	
P18	23	F	16	Epilepsy surgery	R - rostral PFC	47	32.13	
P19	54	M	22	Ischemic stroke	R - IFG / MFG white matter	48	60.11	
P20	71	M	17	Hemorrhage RA	L - rostral PFC / VMPFC*	91	37.06	
P21	23	F	15	Epilepsy surgery D	R - rostral PFC	36	37.79	
P22	27	F	9	Epilepsy surgery	L - lateral rostral PFC*	30	16.45	+ +
P23	26	F	13	Epilepsy surgery D	L - precentral gyrus	19	2.95	
P24	32	F	14	Epilepsy surgery	L - posterior medial PFC	4	14.81	
P25	59	F	16	Hemorrhage RA	L - VMPFC	9	0.87	

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P26	26	F	13	Hemorrhage	L - posterior IFG	32	29.19		
P27	58	M	12	Ischemic stroke	L - precentral sulcus	3	1.22		
P29	75	F	12	Hemorrhage S	L - rostral PFC*	16	14.1	+	+

* indicates patients belonging to the 'damaged left rlPFC' group as defined anatomically. Ischemic strokes affected the middle cerebral artery territory. Hemorrhages were caused by a ruptured aneurism (RA), or due to a spontaneous hematoma (S), or to a vascular malformation for one patient (P26). Epileptic patients underwent a surgical resection of their epileptic focus, whose origin was cryptogenic, except for two patients who had a dysplasia removed (D). Education level corresponds to the number of years since beginning of school (usually at age 6; 12 years correspond to a high school degree). Interval is the delay between lesion and testing in months. 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; Rostral PFC+: damage to rostral PFC extending to anterior part of MFG, SFG, IFG;

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Table 2: Descriptive data, neuropsychological scores, analogy performance, and statistical group comparisons between the 'VLSM Analogy group' and 'other patient group'.

	'VLSM Analogy group' (*n* = 5)	**'Other patient group' (*n* = 22)**	**Statistical comparisons**
Descriptive data: Mean (SD)			
Age (years)	55.40 (18.93)	45.36 (14.75)	U = 34.0, ns
Education (years)	11.20 (5.12)	14.91 (3.08)	U = 25.0, ns
Lesion volume (cc)	55.20 (56.12)	27.40 (21.89)	U = 37.0, ns
Lesion-testing delay (months)	68.8 (38.11)	53.45 (45.91)	U = 42.0, ns
Neuropsychological data: Mean (SD)			
FAB (/18)	15.20 (0.84)	15.82 (1.79)	U = 36.5, ns
Semantic fluency	30.00 (7.84)	27.91 (7.83)	U = 49.5, ns
Lexical fluency	19.60 (5.13)	19.86 (7.46)	U = 47.5, ns
Stroop interference	-3.81 (1.56)	1.56 (5.22)	***U = 9.0, P = 0.002***
Experimental conditions: Mean % (SD)			
MatchApply	87.14 (6.49)	92.69 (8.85)	U = 25.0, ns
MatchFind	86.43 (7.74)	89.29 (12.42)	U = 36.0, ns
AnalogyApply	61.72 (14.31)	79.78 (11.90)	***U = 10.5, P = 0 .003***
Cross trials	61.67 (14.78)	77.18 (13.27)	***U = 21.5, P = 0.035***
Intra trials	61.67 (15.13)	82.20 (13.37)	***U = 10.5, P = 0.003***
AnalogyFind	53.75 (9.81)	76.20 (10.24)	***U = 7.0, P = 0.001***
Cross trials	44.52 (18.74)	70.30 (14.51)	***U = 16.5, P = 0.014***
Intra trials	61.67 (9.03)	81.63 (9.24)	***U = 7.0, P = 0.001***
Indices			
Analogy index	-41.30 (20.04)	-15.79 (8.56)	***U = 9.0, P = 0.002***
Find index	-7.75 (8.94)	-4.41 (6.97)	U = 39.0, ns
Cross index	-17.53 (25.14)	-11.21 (11.46)	U = 50.5, ns

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Values are means (SD) or mean percentage of correct responses (SD) for experimental tasks. Exact *P* values significant at a $P < 0.05$ are provided. FAB: frontal assessment battery; VLSM : voxel-lesion based symptom mapping; ns: non significant.

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Table 3. Impact of tract disconnection on age, education, lesion volume, delay between lesion and testing, and analogy performance.

Tracts were defined a priori based on Aichelburg *et al*., 2014.

	Age (years)	Education (years)	Lesion volume (cc)	Lesion-testing delay (months)	Match mean (%)	Analogy mean (%)	Analogy-index	Find-index	Cross-index
Left									
IFOF-L	U = 51.5, ns	U = 81.0, ns	U = 79.0, ns	U = 84.5, ns	U = 60.0, ns	***U = 36.6, P = 0.008***	***U = 39.0, P = 0.012***	U = 84.0, ns	***U = 47.5, P = 0.038***
Disconnected (*n* = 12)	53.50 (16.96)	13.83 (4.51)	37.19 (39.20)	57.17 (46.87)	90.08 (4.40)	68.92 (12.30)	-27.86 (17.43)	-5.64 (8.78)	-18.50 (15.57)
Intact	42.20 (13.09)	14.53 (3.09)	28.84 (24.55)	55.60 (46.52)	90.40 (11.31)	78.33 (12.49)	-14.63 (9.58)	-4.54 (6.14)	-7.49 (11.87)
UF-L	***U = 39.0, P = 0.014***	U = 83.0, ns	U = 79.0, ns	U = 80.5, ns	U = 57.0, ns	***U = 35.0, P = 0.007***	***U = 35.0, P = 0.008***	U = 78.0, ns	U = 55.5, ns
Disconnected (*n* = 11)	56.00 (15.29)	13.91 (4.72)	37.91 (41.03)	59.45 (48.45)	89.82 (4.51)	68.09 (12.55)	-28.83 (17.94)	-6.00 (9.11)	-18.00 (16.22)
Intact	41.19 (13.28)	14.44 (3.01)	28.86 (23.72)	54.13 (45.33)	90.56 (10.95)	78.31 (12.06)	-14.79 (9.28)	-4.35 (5.98)	-8.52 (12.19)
FMT-L	U = 49.0, ns	U = 68.0, ns	U = 51.0, ns	U = 76.5, ns	***U = 39.0, P = 0.029***	***U = 30.5, P = 0.008***	***U = 34.0, P = 0.015***	U = 59.0, ns	U = 54.5, ns
Disconnected (*n* = 9)	54.44 (16.53)	13.56 (5.20)	45.72 (41.55)	56.89 (43.96)	88.67 (4.15)	66.00 (13.03)	-30.78 (19.46)	-7.37 (9.05)	-18.49 (18.04)
Intact	43.61 (14.40)	14.56 (2.85)	25.97 (23.83)	56.00 (47.91)	91.06 (10.38)	78.22 (11.34)	-15.38 (8.88)	-3.85 (6.20)	-9.33 (11.73)
ATR-L	U = 79.0, ns	U = 81.0, ns	U = 86.0, ns	U = 84.0, ns	U = 54.5, ns	***U = 38.0, P = 0.009***	U = 57.0, ns	U = 85.0, ns	***U = 46.5, P = 0.03***
Disconnected (*n* = 14)	49.07 (17.83)	13.86 (4.20)	34.60 (36.61)	59.00 (48.69)	88.71 (7.80)	69.29 (11.94)	-25.40 (17.30)	-5.49 (8.57)	-18.19 (14.53)
Intact	45.23 (13.49)	14.62 (3.25)	30.35 (26.25)	53.38 (44.21)	91.92 (9.77)	79.38 (12.58)	-15.25 (10.05)	-4.53 (5.94)	-6.13 (11.98)
AF-L	U = 53.0, ns	***U = 17.5, P = 0.016***	U = 52.0, ns	U = 53.5, ns	U = 54.5, ns	U = 44.0, ns	U = 42.0, ns	U = 44.0, ns	U = 30.0, ns
Disconnected (*n* = 5)	46.00 (19.60)	10.80 (3.35)	47.96 (61.66)	55.20 (55.12)	92.00 (3.46)	68.20 (17.88)	-31.93 (25.20)	-2.83 (6.23)	-21.96 (15.54)
Intact	47.50 (15.23)	15.00 (3.41)	29.05 (20.87)	56.55 (44.89)	89.86 (9.61)	75 50 (11.84)	-17.92 (10.81)	-5.52 (7.56)	-10.21 (13.66)
Right									
IFOF-R	U = 69.0, ns	U = 80.5, ns	***U = 48.0, P = 0.05***	U = 84.0, ns	U = 78.5, ns	U = 62.0, ns	U = 73.0, ns	U = 75.0, ns	U = 50.0, ns
Disconnected (*n* = 11)	44.09 (13.54)	14.18 (3.34)	40.05 (21.79)	51.55 (38.39)	90.64 (10.32)	77.36 (13.43)	-16.53 (11.23)	-3.94 (6.69)	-5.79 (12.81)

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Intact	49.38 (17.13)	14.25 (4.07)	27.39 (36.53)	59.56 (51.20)	90.00 (7.91)	71.94 (12.77)	-23.25 (16.81)	-5.77 (7.81)	-16.91 (14.14)
UF-R	U = 88.0, ns	U = 76.5, ns	***U = 44.0, P = 0.025***	U = 70.0, ns	U = 75.5, ns	U = 74.0, ns	U = 89.0, ns	U = 84.0, ns	U = 65.5, ns
Disconnected (*n* = 11)	45.55 (14.71)	14.00 (3.55)	44.06 (38.45)	58.82 (42.38)	91.36 (10.19)	76.09 (14.50)	-19.36 (13.86)	-5.24 (6.92)	-7.33 (13.00)
Intact	48.38 (16.73)	14.38 (3.95)	24.63 (23.89)	54.56 (49.27)	89.5 (7.93)	72.81 (12.29)	-21.31 (16.02)	-4.87 (7.77)	-15.86 (14.80)
FMT-R	U = 57.5, ns	U = 55.5, ns	***U = 20.0, P = 0.002***	U = 67.5, ns	U = 61.0, ns	U = 57.5, ns	U = 63.0, ns	U = 63.0, ns	U = 53.0, ns
Disconnected (*n* = 8)	42.88 (15.97)	15.50 (2.83)	49.29 (17.51)	47.75 (36.92)	93.13 (4.79)	79.25 (7.32)	-16.18 (8.66)	-3.49 (6.93)	-5.58 (15.01)
Intact	49.05 (15.66)	13.68 (3.99)	25.50 (33.73)	59.89 (49.51)	89.05 (9.86)	72.00 (14.47)	-22.33 (16.76)	-5.67 (7.53)	-15.25 (13.63)
ATR-R	U = 82.5, ns	U = 83.5, ns	***U = 48.0, P = 0.041***	U = 73.5, ns	U = 65.5, ns	U = 52.0, ns	U = 67.0, ns	U = 88, ns	***U = 46.5, P = 0.033***
Disconnected (*n* = 15)	46.27 (14.16)	14.47 (3.16)	43.41 (36.60)	62.07 (46.23)	91.53 (9.04)	77.47 (12.88)	-17.47 (12.35)	-4.98 (6.70)	-7.14 (11.88)
Intact	48.42 (18.03)	13.92 (4.46)	18.97 (16.71)	49.08 (46.16)	88.67 (8.56)	70.00 (12.60)	-24.31 (17.44)	-5.08 (8.29)	-18.94 (15.20)
AF-R	U = 58.5, ns	U = 34.5, ns	U = 30.0, ns	U = 62.5, ns	U = 37.0, ns	U = 45.5, ns	U = 54.0, ns	U = 42.0, ns	U = 39.0, ns
Disconnected (*n* = 6)	45.67 (15.11)	16.33 (3.01)	48.60 (27.26)	53.50 (40.50)	94.33 (5.85)	79.83 (7.41)	-16.60 (7.98)	-1.89 (4.66)	-4.32 (14.74)
Intact	47.67 (16.21)	13.62 (3.75)	27.96 (31.71)	57.10 (48.07)	89.10 (9.24)	72.52 (13.99)	-21.63 (16.37)	-5.92 (7.75)	-14.69 (13.89)

For each tract, significance of group comparison between patients with tract disconnection and patients without tract disconnection is provided (Mann-Whitney U with significant differences at a Exact $P < 0.05$ are provided). Other values are mean scores (SD) for patients with tract disconnection ('Disconnected') and patients without tract disconnection ('Intact') in the left (L) and in the right (R) hemisphere. IFOF: inferior fronto-occipital fasciculus; UF: uncinate fasciculus; FMT: fronto-marginal tract; ATR: anterior thalamic radiations; AF: long segment of the arcuate fasciculus; -L: left hemisphere; -R: right hemisphere.

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Table 4: Descriptive data, neuropsychological scores, analogy scores for the short version of the task, and statistical comparisons between patients with an impaired versus preserved analogy performance.

	Patients with impaired analogy scores (*n* = 7)	**Patients with preserved analogy scores (*n* = 20)**	**Group comparisons**
Descriptive data: Mean (SD)			
Age (years)	54.43 (17.02)	44.70 (14.84)	U = 44.5, ns
Education (years)	13.14 (5.81)	14.60 (2.78)	U = 52.0, ns
Lesion volume (cc)	48.66 (47.24)	48.18 (21.84)	U = 39.0, ns
Lesion-testing delay (months)	70.14 (0.63)	68.00 (37.40)	U = 45.0, ns
Neuropsychological scores: Mean (SD)			
FAB (/18)	15.57 (1.27)	15.75 (1.80)	U = 57.5, ns
Semantic fluency	30.86 (7.17)	27.40 (7.88)	U = 55.5, ns
Lexical fluency	21.00 (7.30)	19.40 (7.04)	U = 66.5, ns
Stroop interference	-1.66 (4.27)	1.34 (5.35)	U = 36.0, ns
Experimental conditions short version: Mean % (SD)			
MatchFind-short version	87.77 (7.39)	89.11(12.93)	U = 51.5, ns
AnalogyFind-short version	51.33 (9.64)	77.68 (11.67)	***U = 7.0, P < 0.001***
Analogy index- short version	-53.43 (11.71)	-13.67 (11.65)	***U < 1.0, P < 0.001***

Values are mean scores (SD) or mean percentage of correct responses (SD) for the short experimental task. Exact *P* values significant at a $P < 0.05$ are provided. FAB: frontal assessment battery; ns: non significant

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Descriptive data, neuropsychological scores, analogy performance, and statistical comparisons between patients and healthy subjects.

	Patients (*n* = 27)	**Healthy subjects (*n* = 54)**	**Group comparisons**
Descriptive data: Mean (SD)			
Age (years)	47.22 (15.70)	45.83 (14.43)	U = 695.0, ns
Education (years)	14.22 (3.72)	15.44 (3.03)	U = 580.5, ns
Neuropsychological data: Mean (SD)			
MMSE (/ 30)	27.67 (1.80)	29.00 (0.87)	***U = 411.0, P = 0.001***
FAB (/ 18)	15.70 (1.66)	16.70 (1.18)	***U = 459.0, P = 0.005***
Semantic Fluency	28.30 (7.73)	38.13 (8.82)	***t* = 4.92, *P* < 0.001**
Lexical Fluency	19.81 (7.00)	26.91 (8.08)	***t = 3.89, P < 0.001***
Stroop interference	0.57 (5.19)	4.53 (7.96)	***t = 2.69, P = 0.009***
Short PPT (/ 40)	39.41 (.80)	39.06 (1.29)	U = 665.0, ns
Short naming (/ 40)	38.93 (1.07)	38.96 (1.35)	U = 677.0, ns
Main Analogy and Match scores: Mean % (SD)			
MatchApply	91.67 (8.64)	94.25 (7.95)	U = 564.0, ns
MatchFind	88.76 (11.62)	93.19 (7.08)	U = 551.0, ns
AnalogyApply	76.43 (14.03)	86.54 (9.53)	***U* = 373.0, *P* < 0 .001**
AnalogyFind	72.04 (13.36)	84.27 (9.94)	***U* = 301.0, *P* < 0 .001**
Averaged performance per task and condition			
Match mean	90.21 (8.84)	93.72 (6.08)	***U* = 507.0, *P* = 0 .025**
Analogy mean	74.23 (13.05)	85.41 (8.96)	***U* = 314.0, *P* < 0 .001**
Apply mean	82.23 (10.58)	89.50 (7.90)	***U* = 394.0, *P* = 0 .001**
Find mean	78.40 (11.36)	87.69 (7.73)	***U* = 326.5, *P* < 0 .001**
Indices			

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Analogy index	-20.52 (14.93)	-9.63 (9.27)	***U* = 318.0, *P* < 0.001**
Find index	-5.03(7.30)	-2.03 (7.53)	*U* = 576.0, ns

Values are means (SD) or mean percentage of correct responses (SD) for experimental tasks. Exact *P* values significant at a $P < 0.05$ are provided. MMSE: Mini Mental State Examination; FAB: Frontal Assessment Battery; PPT: Pyramid and Palm Tree Test; ns: non significant.

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Supplementary Method 1: Neuropsychological testing

With respect to semantic fluency, the participants were instructed to name as many animals as possible within a time limit of 120 seconds, without repetition of the same word. In lexical fluency, the subjects were asked to produce as many words as possible beginning by the letter P during 120 seconds, excluding proper nouns and without repetition of the same word.

The Stroop test includes three conditions that were performed in the following order: word reading, colour naming and conflict, which were presented for 45 seconds each. Interference sensitivity was measured by subtracting the predicted interference (calculated from the colour denomination and word reading conditions) and the score obtained at the conflict condition.

Semantic knowledge was assessed using short French versions of a naming test and a semantic matching test adapted from the Pyramid and Palm tree test (Merck *et al.*, 2011). In the short naming test, the subjects were asked to name drawings of 40 objects that belonged to different categories. In the short semantic matching test, which is adapted from the Pyramid and Palm tree test, the subjects were presented with 40 trials of three different written words and were told to match a target word (e.g., “swan”) with one of the two other words with which it is semantically associated (e.g., “pond” and “tree”).

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Supplementary Method 2: Experimental procedure

All trials followed the same design. The instructions were displayed for 4 seconds, followed by a first set of stimuli on the left part of the screen (the source set) for 2 seconds and, then, by two other sets on the right part of the screen (the targets sets). The participants selected the correct target set by a button press on a keyboard within the 11.5 seconds following the target set display. The participants were asked to choose the target set that matched the source set based on the relationships between the stimuli that composed the sets (Analogy tasks) or based on the similarity of their visual features (Match tasks). The stimuli were letters, numbers or abstract symbols, presented in different colours, sizes or patterns. Feedback was given by displaying for 0.5 seconds a green circle for correct answers or a red circle otherwise. The trials were spaced by a 5-second interval.

The experimental procedure began by reading the written instructions to the participants and then training them on all conditions during 26 trials. All participants understood the instructions and were able to perform the tasks correctly after the training. Then, the participants completed one session under each experimental condition in the following order: MatchApply, MatchFind, AnalogyApply and AnalogyFind trials. The AnalogyApply and AnalogyFind sessions both contained 48 consecutive trials (16 trials for each of the three analogy schemas, each including eight intra-dimension and eight cross-dimension analogy trials), and the Match sessions contained 28 trials each. The participants completed the sessions in the following order: 28 MatchApply, 28 MatchFind, 48 AnalogyApply and 48 AnalogyFind trials. The trials were randomized within each session.

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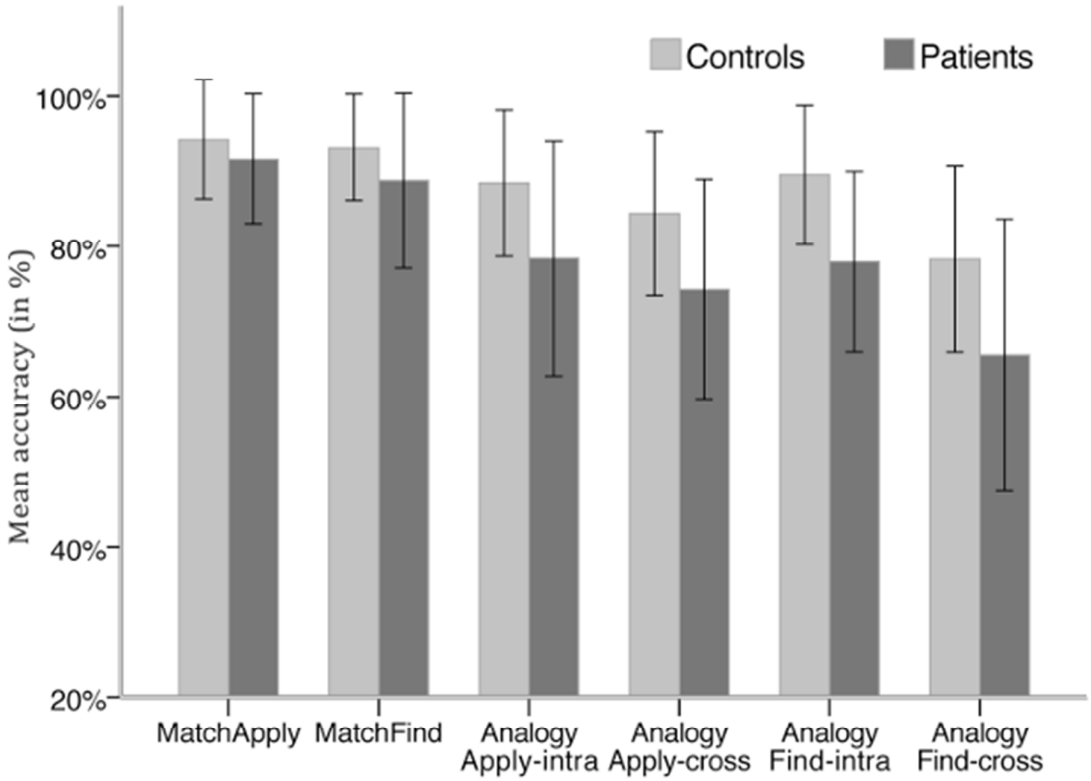
Supplementary Fig. 1: Patients and controls performance under each experimental condition.



Mean accuracy (in %) and SD (error bars) in each experimental condition are displayed for patients (in dark gray) and controls (in light gray).

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Supplementary Table 2: Descriptive data, neuropsychological scores, and statistical comparisons between left brain-damaged and right brain-damaged patients.

	Left lesion (*n* = 14)	**Right lesion (*n* = 9)**	**Group comparisons**
Descriptive data: Mean (SD)			
Age (years)	50.1 (17.6)	41.8 (14.6)	U = 43.5, ns
Education (years)	13.9 (4.3)	15.7 (3.0)	U = 47.0, ns
Lesion volume (cc)	29.7 (38.4)	40.0 (25.5)	U = 42.0, ns
Lesion-testing delay (months)	58.4 (49.4)	68.0 (44.5)	U = 55.0, ns
Neuropsychological data: Mean (SD)			
FAB (/18)	15.9 (1.5)	16.1 (1.5)	U = 53.5, ns
Semantic Fluency	27.6 (8.6)	32.6 (3.9)	U = 37.5, ns
Lexical Fluency	19.5 (8.3)	21.7 (3.9)	U = 48.5, ns
Stroop interference	0.04 (4.8)	1.4 (6.8)	U = 45.5, ns

Values are means (SD). Exact *P* values significant at a $P < 0.05$ are provided. FAB: frontal assessment battery; ns: non significant

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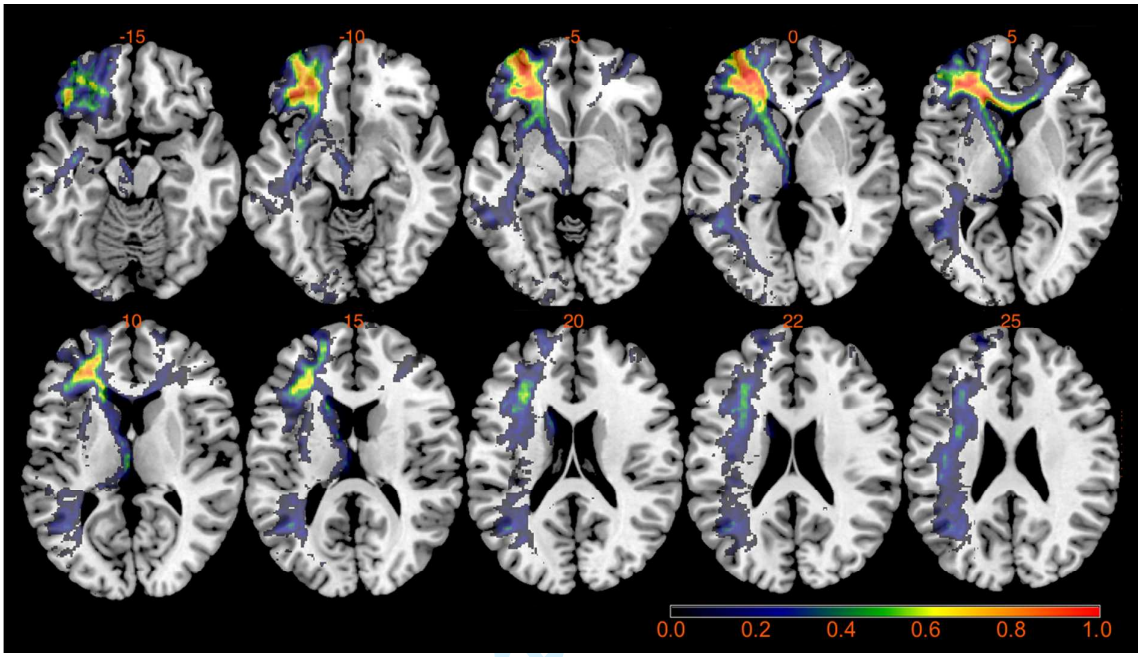
Supplementary Fig. 2. The VLSM connectome map.



The map displays the probablility of connection to the 'VLSM Analogy region' (the tracts passing through the 'VLSM Analogy region') superimposed on a MNI template. This map was built by using the Disconnectome map software as part of the BCB toolkit (http://www.brainconnectivitybehaviour.eu/).

Z coordinates of each slice are given in red ranging from z = -15 to z = 25. The probability of connection to the 'VLSM Analogy region' is color coded.

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Supplementary Table 3. Probability of each lesion to intersect the VLSM connectome map and number of tracts connected to the 'VLSM Analogy region' for each patient / lesion.

Values were obtained using the Tractotron software as part of the BCB toolkit (http://www.brainconnectivitybehaviour.eu/).

	Probability of each lesion intersecting the VSLM connectome map	Number of disconnected tracts among those connecting the 'VLSM Analogy region'
P01	0.0000	0
P02	1.0000	8
P03	0.3787	4
P04	1.0000	8
P05	0.6225	0
P06	0.0000	0
P08	1.0000	8
P09	0.6225	0
P10	0.4774	6
P11	0.3337	0
P12	0.5657	1
P13	1.0000	6
P14	0.5157	0
P15	0.6370	0
P16	0.9999	8
P17	0.8729	6
P18	0.6225	0
P19	0.5189	0

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P20	1.0000	8
P21	0.5124	0
P22	1.0000	8
P23	0.1961	3
P24	0.1000	3
P25	0.1927	4
P26	0.7597	5
P27	0.1763	1
P29	1.0000	8

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Supplementary Table 4. Descriptive data, neuropsychological scores, performance at the short version of the experimental tasks, and statistical comparisons between patients with a left rlPFC damage ('Damaged left rlPFC' group) and patients without a left rlPFC damage ('Intact left rlPFC' group).

	'Damaged left rlPFC' group (*n* = 7)	**'Intact left rlPFC' group (*n* = 20)**	**Group comparisons**
Descriptive data: Mean (SD)			
Age (years)	55.43 (17.86)	44.35 (14.26)	U = 41.5, ns
Education (years)	13.57 (6.00)	14.45 (2.72)	U = 61.5, ns
Lesion volume (cc)	48.66 (47.24)	26.91 (22.90)	U = 47.0, ns
Lesion-testing delay (months)	70.14 (0.63)	51.45 (47.45)	U = 47.0, ns
Neuropsychological data: Mean (SD)			
FAB (/18)	15.43 (1.40)	15.80 (1.77)	U = 53.5, ns
Semantic Fluency	31.57 (7.09)	27.15 (7.77)	U = 47.0, ns
Lexical Fluency	22.29 (6.85)	18.95 (7.01)	U = 58.5, ns
Stroop interference	-1.76 (4.22)	1.38 (5.34)	***U = 34.0, P = 0.047***
Experimental conditions: Mean % (SD)			
MatchFind - short version	86.73 (6.43)	89.46 (13.03)	U = 41.0, ns
AnalogyFind -short version	52.39 (11.50)	77.31 (12.00)	***U = 10.5, P < 0.001***
Analogy index - short version	-50.83 (16.23)	-14.58 (12.99)	***U = 6.5, P < 0.001***

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Values are means (SD) or mean percentage of correct responses (SD) for experimental tasks. Exact *P* values significant at a $P < 0.05$ are provided. FAB: Frontal Assessment Battery; ns: non significant.

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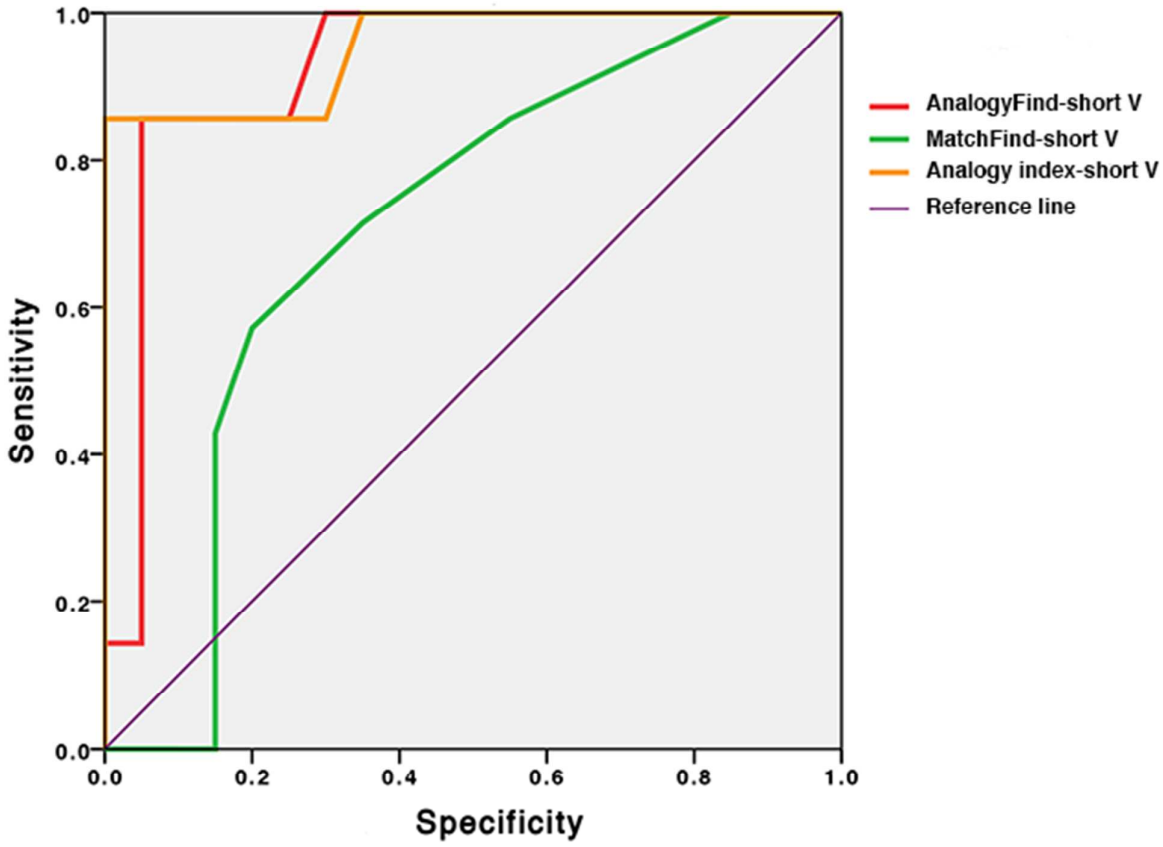
Supplementary Fig. 3: Receiver Operating Characteristic (ROC) curves of the short version of the experimental tasks to discriminate patients with intact versus damaged left rlPFC.



Sensitivity on the Y axis and specificity on the X axis of the short version of the analogy task are displayed for the AnalogyFind-short version condition in red, the MatchFind-short version condition in green and the Analogy index-short version in orange. The reference line is represented in violet.

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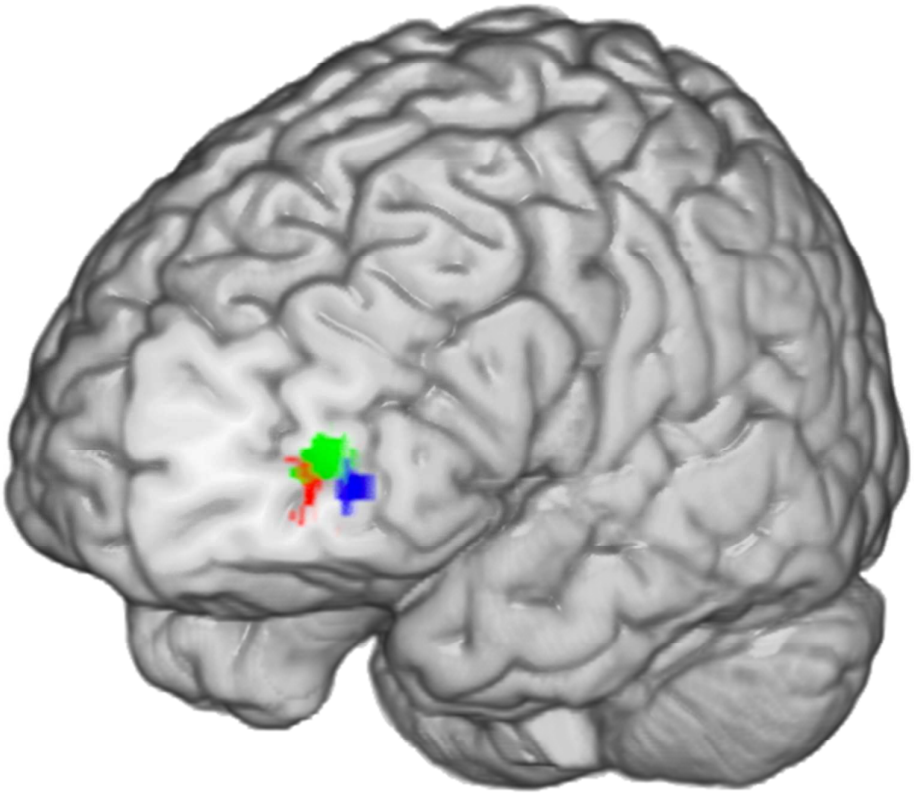
Supplementary Fig. 4: Superimposition of the current result with results from other approaches that used the same analogy tasks.



Overlap of the VLSM Analogy map (red), a VBM map of brain regions which structure correlated with analogy performance in healthy subjects (Aichelburg *et al.,* 2014; green) and a sphere centred on the peak maxima observed in a functional imaging study using the same tasks (Volle *et al.,* 2010; blue).

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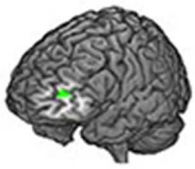

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