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Abstract

Analogical reasoning is critical for making inferences and adapting to novelty. It can be studied experimentally using tasks that require creating similarities between situations or concepts, i.e., when their constituent elements share a similar organization or structure. Brain correlates of analogical reasoning have mostly been explored using functional imaging that has highlighted the involvement of the left rostrolateral prefrontal cortex (rlPFC) in healthy subjects. However, whether inter-individual variability in analogical reasoning ability in a healthy adult population is related to differences in brain architecture is unknown. We investigated this question by employing linear regression models of performance in analogy tasks and voxel-based morphometry in 54 healthy subjects. Our results revealed that the ability to reason by analogy was associated with structural variability in the left rlPFC and the anterior part of the inferolateral temporal cortex. Tractography of diffusion-weighted images suggested that these two regions have a different set of connections but may exchange information via the arcuate fasciculus. These results suggest that enhanced integrative and semantic abilities supported by structural variation in these areas (or their connectivity) may lead to more efficient analogical reasoning.

"When a man sits with a pretty girl for an hour, it seems like a minute. But let him sit on a hot stove for a minute and it's longer than any hour. That's relativity" (Einstein 1938).

This metaphorical quote from Albert Einstein illustrates how an analogy can be employed to make the concept of relativity a little more comprehensible to the layman. To understand this metaphor, we employ analogical reasoning to identify similarities between a familiar situation (variations in time estimation according to the pleasantness of a personal experience) and a new or complex one (variation in space and time according to the referential of the observant). Analogical reasoning uses these similarities to make inferences about a novel situation or concept and to infer rules and implications (Gentner and Holyoak 1997). Analogical reasoning is therefore critical for adapting to novelty, and for learning, explaining or conceiving new concepts, and is thought to constitute a cognitive basis for fluid intelligence (Holyoak and Thagard 1995; Geake and Hansen 2005; Hofstadter and Sander 2013).

Analogical reasoning is considered a form of relational reasoning, as similarities concern the relationships between the elements of a situation or an object rather than these elements themselves (Blanchette and Dunbar 2000; Christoff et al. 2009; Markman and Gentner 2000). These relationships describe particular aspects of the ‘‘structure’’ of an object/situation (or how the elements are organized in an object/situation). Cognitive theories assume that analogy processing includes the generation of mental representations of the relationships (their structure) and their mapping based on their similarities, which is distinct from the mapping of stimuli based on non-relational item-to-item similarity (Blanchette and Dunbar 2000; Holyoak and Morrison 2012; Holyoak and Thagard 1995; Markman and Gentner 2000; Markman and Gentner 1993). Processes allow for the generation of a schema for the whole analogy, i.e., a general relational

concept of the common structure. In this sense, analogical reasoning includes a conceptual dimension that is not present in purely perceptual similarity matching.

An analogy schema can be inferred from the mapping of several exemplars sharing a similar structure (exemplar-based). For instance, in two sets of three different letters, an analogy schema (i.e., a relational concept) can be produced through a similarity between sets that show a similar pattern of 'increase in size', i.e., by noting that in both sets the first letter is smaller than the second one and that the second one is smaller than the third one. Alternatively, when the schema is familiar, it can be retrieved from memory based on only one familiar exemplar or on a verbal description (e.g. 'increase in size'), i.e. a relational term describing the conceptual analogy (concept-based) (Gentner and Medina 1998). An exemplar-based analogy requires the induction of the analogy schema, whereas in concept-based analogy the analogy schema is given with the instruction. Whether exemplar-based and concept-based analogical reasoning processing is supported by different brain structures is unknown. Studies of inductive reasoning nevertheless suggest that the left lateral prefrontal cortex is important for inferring abstract rules (Reverberi et al. 2005a; 2005b), such as analogy schemas.

Functional imaging studies of analogical reasoning have shown a set of frontal and parietal regions engaged during analogy tasks (Wharton et al. 2000; Christoff et al. 2003; Bunge et al. 2005, 2009; Geake and Hansen 2005, 2010; Green et al. 2006, 2010, 2012; Cho et al. 2010; Wendelken et al. 2008, 2012; Krawczyk et al. 2010a; Volle et al. 2010; for a review Krawczyk 2012). The fronto-parietal network involved in analogical reasoning has been associated with the executive or working memory aspects of analogy tasks and with fluid reasoning (Jung and Haier 2007; Geake and Hansen 2010; Preusse et al. 2011). The parietal component may be involved in processing the visuospatial relationships between multiple objects (Watson et al. 2012) or in the

organization of maintained information (Wendelken et al. 2008). Caudal prefrontal regions may support the inhibition of interference (Morrison et al. 2004, Krawczyk et al. 2008; Cho et al. 2010; Thibaut et al. 2010b), or the controlled retrieval or selection of information in semantic memory (Bunge et al., 2005). A few patient studies have demonstrated the critical role of the PFC in analogical reasoning (Krawczyk et al., 2008; Morrison et al., 2004) and additionally suggested that the temporal cortex may play a significant role in analogical reasoning by activating the semantic relation that links the terms of the analogy (Morrison et al., 2004; Schmidt et al., 2012). Among the regions that have been associated with analogical reasoning, the left rostrolateral prefrontal cortex (rlPFC) is the most consistently activated in functional imaging, as demonstrated in a recent meta-analysis of 10 functional imaging studies on analogy (Vartanian 2012). The rostral PFC component is thought to support the simultaneous comparison and/or integration of multiple relations between stimuli, the integration of the results of separate cognitive operations (Ramnani and Owen 2004; Christoff et al. 2001; Kroger et al. 2002; Wendelken et al. 2008; Bunge et al. 2005; 2009; Cho et al. 2010; Hampshire et al. 2011), or high levels of abstract thinking (Christoff et al. 2009). Previous works have also suggested that the rostral PFC may be recruited before exemplars are compared (Volle et al. 2010; Krawczyk et al. 2010a), bringing its role in exemplar-based analogy into question. The exact role of this region in distinct analogy processes such as integration of relationships, mapping, schema induction, and its relationship to analogy performance remain unclear.

Analogical reasoning is indeed a complex and highly adaptive cognitive function marked with a large variability in individual ability. Studies in children and adolescents previously suggested that the development of analogical reasoning abilities with age is related to executive functions (Thibaut et al. 2010a; 2010b) and to changes in rlPFC activation and structure (Crone

et al. 2009; Dumontheil et al. 2010; Krawczyk et al. 2010b). Although evidence from activation studies is increasing in adults, the relationship between the morphology of the PFC (or other brain regions) and an individual's capacity to reason by analogy remains unexplored. In other words, can inter-individual variations in analogy ability be linked to individual variations in regional structures of the brain?

Brain local morphology is classically measured using voxel-based morphometry (VBM; Ashburner and Friston 2000; Good et al. 2001; Kanai and Rees 2011) and can be statistically related to behavioral measures. Previous morphometry studies have shown correlations between individual performance in other relational reasoning tests, such as IQ tests reflecting fluid intelligence, and grey matter (GM) local morphology in the rlPFC (Frangou et al. 2004; Haier et al. 2004; Colom et al. 2006, 2009; Narr et al. 2007; Yuan et al. 2012), and between analogical reasoning capacity and the structure of the developing brain, but have not explored analogical reasoning in adults. Whether rlPFC structural variability in adults relates to variable performance in analogical reasoning (a particular type of relational reasoning) and to the processes engaged when forming the analogy remains to be demonstrated.

To address this question, we performed a voxel-wise analysis to correlate local brain volumes with analogical reasoning performance. To distinguish between the relational processing component and the schema induction component of analogical reasoning, we manipulated our analogy tasks to distinguish analogies based on exemplar comparison (exemplar-based analogies requiring schema induction) from analogical reasoning based on a relational term (concept-based analogies in which an analogy schema is provided to the participants, for instance 'increase', without a need to infer it). We used a control-matching task based on the similarity of perceptual features in order to control for non-relational mapping

processing. We explored the anatomical connectivity of the regions associated with these tasks using diffusion-based tractography to provide further understanding about their potential interactions and roles in analogy processing.

Methods

Participants

Fifty-seven volunteers were initially included in this study, but three of them were excluded from the analysis for medical reasons (anomalies on neuropsychological testing or on the brain MRI). Thus, fifty-four right-handed native French speakers (27 females; age 22 - 71 years, mean 45.8 ± 14.4 years) participated in the morphometry study. A large age range was chosen in order to include a group of unselected participants with enough variability to represent the human diversity in the general population. The advantages of such an approach have been discussed previously (Colom et al., 2007; Haier et al., 2004; Goh et al., 2011; Grogan et al., 2009). Neuropsychological and radiological data were carefully screened. All participants were healthy adults with no history of neurological or psychiatric disorders and no cognitive impairments or depression, as assessed using translated versions of the Mini Mental state (Folstein et al. 1975) and the MADRS (Montgomery-Asberg Depression Scale; Montgomery and Asberg 1979) as well as the Frontal Assessment battery (Dubois et al. 2000). All brain images were examined by a neuroradiologist. Millimetric T1-weighted and diffusion weighted images showed no significant signal abnormalities evocative of a small vessel disease or of an evolving neurological disease. Subjects with MRI pathological abnormalities were excluded. Participants had an average of 15.4 ± 3.0 years of education (range 10 - 26).

The local ethics committee approved the experiment, and all participants provided written informed consent.

Of the 54 participants, 47 (24 males; mean age 45.5 ± 14.8 years; mean education level 15.4 ± 3 years) were included in the connectivity study using diffusion images. Data from the remaining 7 participants could not be analyzed because of technical problems with the diffusion images.

Experimental Procedure (Figure 1)

The experimental paradigm consisted of four experimental conditions: two tasks (Analogy and Match) each having an exemplar-based condition ('Find') and a concept-based or rule-based condition ('Apply') as described below. The participants were trained on the two analogy (named AnalogyApply and AnalogyFind) and two match (MatchApply and MatchFind) conditions for 26 trials. All subjects understood the instructions and were able to perform the tasks correctly after the training. Then, each condition was implemented in blocks in the following order: 28 MatchApply, 28 MatchFind, 48 AnalogyApply and 48 AnalogyFind trials. The trial order was randomized within each block. In each trial, instructions were displayed for four seconds. Immediately afterward, a left set of stimuli (source set) was displayed for 2 seconds followed by the display of the two comparison sets on the right (target sets). The participants were required to judge which of the two target sets shared similarities with the source set on criteria indicated by the instructions of the task condition. The source and target sets consisted of groups of letters, numbers, or abstract symbols in different colors, sizes, or patterns. The sets were equivalent in terms of visual and temporal features between the task conditions. The participants had 11.5 seconds to respond by pressing the up or down arrow key.

A signal appeared 1.5 seconds before the end of the display. Feedback was displayed for 0.5 seconds, a green circle indicated a correct answer and a red circle an incorrect answer. The trials were separated by a 5-second interval.

Behavioral Task (Figure 1)

The Analogy and control Match tasks employed were adapted from a previous study (Volle et al. 2010). The participants had to choose the target sets that shared similarities with the source set, based on the relationships between the stimuli (the schema; Analogy task), or based on a shared perceptual attribute (Match task). Hence, this experimental design allowed for the study of the participants' performance of finding or applying an abstract analogy schema (concept) while controlling for their performance in finding or applying a perceptual (concrete) similarity.

Six diverse attributes were used as matching rules in the Match task, namely color, quantity, size, texture, figures and letters. In the Analogy task, 6 distinct schemata were employed, namely proportion, subtraction, addition, mirroring, symmetry and progression (see supplementary Figure S1 for a sample of trials). As described in Volle et al. (2010) and illustrated in supplementary Figure S1, half of the Analogy trials were intra-dimension analogies, and half were cross-dimension analogies. In the intra-dimension task, the analogy schema concerned the same dimension in the source and target sets (e.g., an increase in the size of the stimuli in both the source and the target). In the cross-dimension task, the analogy concerned different dimensions (for instance, an increase in the size of the stimuli in the source and an increase in the color lightness of the target stimuli).

Original Analogy and Match tasks were further modified in order to differentiate exemplar-based and concept-based analogical processing. In the original exemplar-based Analogy condition (as used in Volle et al. 2010, here named AnalogyFind), participants had to find the relational schema by considering the structures of each exemplar set, comparing them and finding their similarities (i.e., it was an internally generated analogy with relational processing and concept formation/induction). The instruction "find analogy" was displayed, and the task was solved by comparing the sets (Figure 1, top left). In the new concept-based Analogy task, here named AnalogyApply condition, the relational schema was explicitly given to the subjects using a verbal term displayed on the screen (as for instance "mirror image" in Figure 1, bottom left). They had to consider and compare the multiple relationships between stimuli, but there was no need to form or retrieve the schema (i.e., it was an externally driven analogy with relational processing but without schema induction). The three analogy schemas used in the AnalogyFind condition, were distinct from the three schemas used in the AnalogyApply condition.

The same principle was applied to the Match tasks. In the MatchFind condition, participants had to find the perceptual relationship between the source and correct target set. The instruction "find match" was displayed and the task was solved by comparing the exemplars and finding the matching rule (Figure 1, top right, the similarity concerned the number of stimuli). In the MatchApply condition, the participants were instructed to apply a given matching rule, which was presented verbally. For instance, in Figure 1 (bottom right), "Same Colors" appeared on the screen to instruct the participants to match colors. The three matching rules used in the MatchFind condition, were distinct from the three rules used in the MatchApply condition.

Behavioral Analysis

Accuracy and response times were measured, and statistical analyses were conducted. Repeated measures ANOVA analysis was employed to compare conditions in the 2x2 within-subjects design for the Analogy versus Match task and Find versus Apply conditions using SPSS software (http://www-01.ibm.com/software/analytics/spss/). We also ran Pearson correlation analyses between the age, education, and experimental scores, and compared the performance of males and females using an independent samples t test.

VBM study: Image acquisition and analysis

Structural T1-weighted images

All participants underwent the same high-resolution T1-weighted structural MRI scans acquired on a Siemens 3 Tesla VERIO TIM system equipped with a 32-channel head coil. An axial three-dimensional MPRAGE dataset covering the whole head was acquired for each participant as follows: 176 slices, voxel resolution = 1×1×1 mm, TE = 2.98 msec, TR = 2300 msec, flip angle = 9°.

VBM pre-processing

3D T1-weighted sequences were processed and analyzed with SPM8 (Wellcome Department of Imaging Neuroscience, London, UK) running on Matlab (Mathworks Inc., Natick, MatchApply, USA; www.mathworks.com/matlabcentral). The VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/) was employed to perform MRI data pre-processing (http://dbm.neuro.uni-jena.de/vbm8/BVM8-Manual.pdf). First, the T1 images were spatially normalized to the

MNI152 Dartel template using the high-dimensional Dartel normalization (Ashburner 2007) and were segmented into GM, WM and cerebrospinal fluid using SPM8's new version of the unified segmentation method (new segment; Ashburner and Friston 2005). Default estimation parameters were employed (http://dbm.neuro.uni-jena.de/vbm8/BVM8-Manual.pdf) to compute normalized and modulated GM images with an isotropic voxel size of 1.5 mm3. Modulation compensates for regional volume changes caused by normalization. The "normalized non-linear modulation only" option was used, allowing us to analyze relative differences in regional GM volume corrected for individual brain size. The quality was evaluated by displaying one slice for each image module and searching for visual abnormalities and by checking the sample homogeneity using the covariance between individual images. The images with the lowest covariance (-2 standard deviations) were visually examined, but none of them had to be excluded. In addition, all normalized 3D images were visually inspected and compared to the template using frontal anatomical landmarks by an expert neurologist (E.V.). Modulated and normalized GM images were then smoothed using a Gaussian kernel of 8-mm3 full width half maximum (FWHM) to account for slight variations between individual normalizations and to allow for parametric statistics. After pre-processing, the smoothed, modulated, normalized GM datasets were used for statistical analyses.

VBM whole-brain statistical analysis

To investigate the relationship between VBM regional GM density and various aspects of analogical reasoning, we ran multiple regression analyses in SPM8 between GM volume and Analogy and Match mean scores. Two separate models were used. In the first one, the Find and Apply conditions were averaged so that the mean Analogy score (AnalogyFind and

AnalogyApply) and the mean Match score (MatchFind and MatchApply) were entered as separate covariates in the regression model, enabling the determination of the brain correlates for each task. In the second model, the Analogy and Match scores were collapsed so that the mean score in AnalogyFind and MatchFind conditions ("Find") and the mean score in AnalogyApply and MatchApply conditions ("Apply") were entered as separate covariates in the regression model. Age, gender and education were co-varied out in the linear regression model. Data were also normalized and corrected for individual total GM volume by entering their values as covariates in the linear model. Global values of total GM volume were extracted and calculated from the get_totals script (available on http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m). Threshold masking was set to 0.2 to include in the analysis only voxels with sufficient signal. For each regression analysis, we investigated significant results at $p < 0.001$ uncorrected for multiple comparisons (with a minimal cluster size of 100 voxels). Within the significant clusters, the mean GM volume was extracted using FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and entered as dependent variables in new regression analyses, in which each task condition was a covariate, and age, gender, education and total GM volume were covaried out. Each cluster volume was plotted against performance for illustration purposes.

Next, a *Small Volume Correction* (SVC) for multiple comparisons was applied on the same analyses as described in the following paragraph. This statistical approach of combining uncorrected and corrected results is frequently employed in VBM analysis (Ridgway et al. 2008) and has the advantage of showing both exploratory and hypothesis driven results.

VBM SVC Analyses within Independent Regions of Interest (ROI)

ROIs were selected independently from the whole-brain analysis and located in the most consistent region reported in functional imaging studies: the rlPFC. The left ROI was based on the previous functional brain imaging study by Volle and colleagues (Volle et al. 2010) that demonstrated rostral prefrontal involvement in analogical reasoning when employing a similar task. The analysis was focused on the rlPFC maxima reported in this study of analogy tasks. The ROI was located in the left rostral MFG or BA 10/46 (MNI coordinates: x=-44, y=50, z=-4). We built an 8-mm radius sphere centered on these coordinates and used this ROI for subsequent analyses. Note that this region is very similar to the region reported in the meta-analysis by Vartanian (Vartanian, 2012; MNI-converted coordinates, x=-44.4, y=40.1, z=3.2) and identified as a core region for analogy. To check if analogy processing is associated with bilateral rlPFC morphometry, we built a symmetrical ROI in the right hemisphere with the following coordinates (+44, 50, -4). We ran SVC analyses in these ROIs to investigate significant correlations of each condition with GM volume within these regions. The threshold was set to 0.05 after a *Family Wise Error* correction (fwe) for multiple comparisons.

Connectivity study: image acquisition, preprocessing and analysis

One of the best methods of studying the functional specialization of specific brain regions is to examine the input and output of that region (Van Essen and Maunsell 1983). Therefore, based on the diffusion obtained from 47 of the 54 participants, we explored the connections terminating in and emerging from the brain regions identified by VBM as showing a volumetric change associated with performance in analogical reasoning.

Diffusion images acquisition

A total of 70 near-axial slices were acquired on a Siemens 3-Tesla VERIO TIM system equipped with a 32-channel head coil. We used an acquisition sequence fully optimized for tractography of DWI that provided isotropic (2 × 2 × 2 mm) resolution and coverage of the whole head. The acquisition was peripherally gated to the cardiac cycle with an echo time (TE) of 85 msec. We used a repetition time (TR) equivalent to 24 RR. At each slice location, 6 images were acquired with no diffusion gradient applied. Additionally, 60 diffusion-weighted images were acquired in which gradient directions were uniformly distributed in space. The diffusion weighting was equal to a b-value of 1500 sec/mm^2.

Diffusion imaging pre-processing

Spherical deconvolution was chosen to estimate multiple orientations in voxels containing different populations of crossing fibers (Tournier et al. 2004; Anderson 2005; Alexander 2006). The damped version of the Richardson-Lucy algorithm for spherical deconvolution (Dell'Acqua et al. 2010) was calculated using an in-house developed software. Algorithm parameters were chosen as described before (Dell'Acqua et al. 2013).

Whole-brain tractography was performed by selecting every brain voxel with at least one fiber orientation as a seed voxel. From these voxels and for each fiber, orientation streamlines were propagated using Euler integration with a step size of 1 mm. When entering a region with crossing white matter bundles, the algorithm followed the orientation vector of the least curvature (as described in Schmahmann et al. 2007). Streamlines were halted when a voxel without fiber orientation was reached or when the curvature between two steps exceeded a

threshold of 60°. Spherical deconvolution, fiber orientation vector estimation and tractography were performed using in-house software developed with Matlab 7.8 (http://www.mathworks.com).

Tractography dissections

Significant regions from the whole-brain VBM analyses were used as ROIs for tract dissections. We dissected the tracts connecting the observed ROIs associated with Analogy, Match and Find performance.

For each participant, the convergence speed maps (Dell'Acqua et al. 2013) were registered to the MNI152 template using Advanced Normalization Tools ANTs (Klein et al. 2009). The inverse deformation was then applied to the ROIs to bring them within the native space of every participant.

Binary individual visitation maps were created for the connections emerging from or terminating in the three observed ROIs by assigning each voxel a value of 1 or 0, depending on whether the voxel was intersected by the streamlines of the tract. Binary visitation maps of each of the dissected tracts were normalized to MNI space using the same affine and diffeomorphic deformations as calculated above. We created percentage overlap maps by adding the normalized visitation maps from each subject at each point in the MNI space. Therefore, the overlap of the visitation maps varies according to inter-subject variability. We inspected tracts reproducible in more than 50% of the participants, a method described previously in Thiebaut de Schotten et al. (2011). Tracts resulting from this analysis were visually inspected and identified using an atlas of human brain connections (Rojkova et al. under revision; Thiebaut de Schotten et al. 2011).

Results

Behavioral Results

Accuracy (Figure 2A)

Descriptive statistics revealed systematic errors in a few trials. Less than 50% of the participants (less than chance) gave correct answers to three of the 48 AnalogyApply trials and three of the 48 AnalogyFind trials. Because these trials could have been missed for other reasons than a poor analogical reasoning ability, or because in these trials both target sets could be interpreted as a correct analogy, they were discarded from further statistical analyses, and only the remaining 45 AnalogyApply and 45 AnalogyFind trials were analyzed. Repeated measures ANOVA revealed a significant main effect of task (F (1, 53) = 70.1, p < .001; Match conditions mean = 93.7% of correct responses; Analogy conditions mean = 85.4%) and a marginally significant main effect of concept formation (finding the schema; F (1, 53) = 3.7, p = .06; Apply conditions mean = 89.5%; Find conditions mean = 87.7%). No significant interaction was found between task and concept formation effects, F (1, 53) = 0.7, p < .401. There was no decrease in performance over time in our group of participants.

Response Times (RTs; Figure 2B)

Repeated measures ANOVA revealed a significant main effect of task on RTs (F (1, 53) = 157.4, p < .001; Match conditions mean = 3347 ms; Analogy conditions mean = 4397 ms) and a significant main effect of concept formation (F (1, 53) = 87.0, p < .001; Apply conditions mean

= 3663 ms; Find conditions mean = 4252 ms). A significant interaction was found between task and concept formation effects, F (1, 53) = 45.4, p < .001.

Correlations: Age, Gender & Education

Age was significantly negatively correlated with accuracy in Analogy conditions (AnalogyApply: r = -.287, p = .035; AnalogyFind: r = -.401, p = .003; mean Analogy score: r = -.375, p = .005), but not significantly with accuracy in the Match conditions (MatchApply: r = -.109, p = .433; MatchFind: r = -.195, p = .159; mean Match score: r = -.184, p = .182). A significant gender difference was found for AnalogyFind (t = 2.270, p = .027; mean accuracy for males: 87%, for females: 81%) and for the mean Analogy score (t = 2.218, p = .031; 88% for males and 83% for females) but not for the other conditions (AnalogyApply: t = 1.781; p = .081; MatchApply: t = .424, p = .673; MatchFind: t = -.068, p = .946; mean Match score: t = .238, p = .813). Education was significantly positively correlated with mean accuracy in Analogy conditions (AnalogyApply: r = .463, p < .001; AnalogyFind: r = .318, p < .019; mean Analogy tasks: r = .422, p = .001) and with MatchApply ((r = .270, p = .048), and there was no correlation in MatchFind (r = -.142, p = .306). Correlation was not significant with mean Match score (r = .094, p = .499).

VBM Whole-Brain Analysis: GM Correlations with accuracy in Analogy and Match tasks (Figure 3)

Voxel-wise multiple regression analyses of accuracy by task condition were conducted within GM. Positive correlations were found with Analogy and Match conditions (Table 1). Accuracy

in Analogy tasks (mean score of AnalogyApply and AnalogyFind conditions) was associated with GM volume in the left and right anterior inferolateral temporal cortex (aITG; regions hereafter referred to as lTEMP on the left and rTEMP on the right), while accuracy in Match tasks (mean score of MatchApply and MatchFind conditions) was not associated with a significant region (Figure 3).

Negative GM correlations are reported in Table 2. For accuracy in Analogy tasks, negative correlations with GM volume were found in the left rlPFC (middle frontal gyrus (MFG); BA 10; a region hereafter referred to as lPOL). For accuracy in Match tasks, negative correlations with GM volume were observed within the anterior part of the right inferomedial temporal cortex (fusiform gyrus) (region hereafter referred to as rTEMPmatch) and in the parietal region.

Because age was negatively correlated with performance in Analogy tasks, and because the age range in our participants was large, we searched for correlations between age and GM volume within clusters associated with Analogy performance in the whole-brain analysis. The correlation between age and GM volume within the left rlPFC region (lPOL) was significant and negative (r = -.435; p = 0.001), but it was no longer significant after controlling for the total GM volume (r = -.202, p = .147). Within the anterior temporal region (lTEMP, that correlated positively with analogy accuracy), the correlation between age and GM volume was significant and negative (r = -.296, p = .030), but was not significant when controlling for total GM volume (r = -.161, p = .250).

VBM Whole-Brain Analysis: GM Correlations with "finding the rule" (Figure 3)

Negative GM correlations are reported in Table 2. For accuracy in the Find conditions (mean AnalogyFind and MatchFind accuracy), negative correlations with GM volume were found in the left inferior frontal sulcus (IFS; BA 45) extending to the pars triangularis and the middle frontal gyrus; a region hereafter referred to as lmidPFC. No significant correlation was found with the Apply conditions.

The correlation between age and GM volume within the lmidPFC region was significant and negative ($r = -.642$; $p < .001$), and stayed significant after controlling for the total GM volume ($r = -.388$, $p = .004$).

Regression with the VBM regions (Table 3 and Figure 3)

To better understand the brain correlates to each condition and task, we ran multiple regressions between each region identified in the whole-brain analysis (as dependent variables) and each score separately (AnalogyFind, AnalogyApply, MatchFind and MatchApply being predictors), with age, gender, education and total GM volume as covariates. The plots are presented in Figure 3 and the statistics in Table 3. These analyses show that the Analogy regions (lPOL, rTEMP) are associated with both the AnalogyFind and AnalogyApply scores, and that the Find region (lmidPFC) is associated with both the AnalogyFind and MatchFind scores.

VBM SVC Analysis (Table 4)

To clarify the role of rlPFC in analogy, we looked for significant correlations between GM volume in rlPFC ROIs with mean Analogy and mean Find performance (as in the whole-brain analysis), and additionally with each experimental condition in separate regression models. Left

and right rlPFC ROIs have been drawn *a priori* from fMRI data (Volle et al. 2010). Significant negative correlations were found for accuracy in the AnalogyFind and AnalogyApply conditions and for the mean Analogy score (Table 4) within the left rlPFC ROI, but not in the right rlPFC. For MatchApply and MatchFind conditions and for the Find mean score, no correlation was found within any ROI.

Connectivity patterns of the VBM regions (Figure 4)

Connectome of Analogy regions

The lPOL connectome, representing fibers connecting the left rlPFC VBM region associated with analogy performance, included projection fibers from the anterior fronto-thalamic radiations, commissural fibers from the anterior forceps of the corpus callosum, and several association fibers, namely the Inferior Fronto-Occipital fasciculus (IFOF), the Uncinate fasciculus (UF), the Arcuate fasciculus (AF, long segment) and the Fronto-Marginal tract (FMT).

The lTEMP connectome, representing fibers connecting the left temporal VBM region, was identified as the Inferior longitudinal fasciculus (ILF), the Arcuate fasciculus (AF, long segment), and the tapetum of the corpus callosum. The rTEMP connectome included similar contralateral fasciculi in the right hemisphere.

These findings show that lPOL and lTEMP have distinct anatomical connections but are both connected to the long segment of the AF.

Connectome of Match (control task) region (Figure 4)

The rTEMPmatch connectome (representing fibers connecting the right inferomedial temporal VBM region associated with Match tasks) included the ILF (running medially to the rTEMP connectome), the fornix, and intratemporal connections.

Connectome of Find regions (Figure 4)

The lmidPFC connectome (representing fibers connecting the left lateral caudal prefrontal VBM region associated with finding the matching rule and/or the analogy schema) included mainly intrafrontal fibers along the IFS and inferior frontal gyrus, and possibly some arcuate fibers posteriorly.

Discussion

The current study reveals the novel finding that the structure of brain regions in healthy adults varies according to individual abilities in analogical reasoning. These findings highlight structure-function relationships based on individual variations within the normal range in non-pathological subjects. First, a whole-brain VBM analysis showed a negative correlation between GM volume within the left rlPFC and performance on Analogy tasks. VBM-based cluster analyses and SVC analyses using independent ROIs built from a published study on analogical reasoning demonstrated that the left rlPFC was associated with both exemplar-based and concept-based analogy conditions (AnalogyFind and AnalogyApply). This result argues for a role of the left rlPFC in the analogical processes shared by these conditions but not in the perceptual matching task.

These findings show a strong anatomical convergence with functional imaging. This convergence is of greatest relevance because VBM and functional imaging methods differ in their physiological implications; VBM explores the relationship between brain structure and analogy as variable inter-individual features, while most functional imaging studies that have been performed in this field showed brain regions recruited by all subjects for common analogy processing. These results thus suggest that the rlPFC supports cognitive processes engaged in analogical reasoning and, moreover, that the efficiency of these processes depends on rlPFC morphometry.

In addition to this main result, the whole-brain VBM analysis also pointed to anterior temporal regions, bilateral inferolateral areas being associated with Analogy tasks, while right inferomedial areas were associated with control Match tasks. Tractography showed that these distinct Analogy and Match temporal regions have distinct sets of connections to other regions. These regions may support the distinct semantic and visual processing of information required by Analogy and Match tasks, respectively, as suggested previously (Pascual et al. 2013). Tractography also suggested that the frontal and temporal regions associated with analogy capacity have a different set of connections but share the long segment of the AF that connects both of them.

Altogether, our results suggest that the morphometry of the left rlPFC and anterolateral temporal regions predicts relational reasoning or conceptual abilities rather than perceptual comparisons or similarity identification. As illustrated in Figure S1, perceptual similarities between the source and the target in the Analogy tasks were reduced by varying stimulus attributes such as font, color, position, size, identity, and by introducing cross-dimension analogies in half of the trials. A debriefing questionnaire performed in a previous study that used

the same tasks (Volle et al. 2010) showed that participants were able to verbalize the analogy schemata used in the tasks at the end of the procedure, suggesting that they processed the analogies conceptually rather than perceptually.

Finally, this study dissociates the left rlPFC region associated with the mean Analogy performance (lPOL) from the more posterior lateral PFC region associated with the mean Find performance (lmidPFC). This result suggests that the left rlPFC (lPOL) supports the relational and abstract thinking abilities required in analogical reasoning (but not in attribute matching task), while the left IFG (lmidPFC) is associated with the ability to infer or identify a cognitive rule based on a perceptual (matching rule) or a relational (analogy schema) similarity. The tractography analysis showed that the lPOL and lmidPFC regions had different sets of connections, with lPOL connecting various distant regions while lmidPFC had intra-frontal connections.

The role of each of these regions in analogy and the possible physiological meaning of these new results will be discussed below.

Role of the left rlPFC in analogy

The current findings suggest that the participants' ability in analogical reasoning depends on individual variations in GM volume within the left rlPFC. This result converges with previous findings on the cerebral correlates of analogy using functional imaging (Wharton et al. 2000; Luo et al. 2003; Christoff et al. 2003; Bunge et al. 2005, 2009; Geake and Hansen 2005, 2010; Green et al. 2006, 2010; Wendelken et al. 2008, 2012; Wartenburger et al. 2009; Volle et al. 2010; Cho et al. 2010; Krawczyk et al. 2010a; Preusse et al. 2011; Hampshire et al. 2011;

Vartanian 2012; Watson and Chatterjee 2012). Strikingly, the very same left rlPFC region was observed in functional MRI using similar analogy tasks in different participants (Volle et al. 2010; Figure S2). The experimental design and the results of this study suggest a role for the rlPFC in building a structured mental representation of stimulus sets by considering multiple relationships. The current findings from the SVC analysis (Table 4) in fact suggest that the left rlPFC has a role in analogy even when the relational concept is explicitly given (AnalogyApply) and thus there is no need to find or infer the schema, i.e., no need for concept induction. Both Analogy conditions still require the processing of relationships between stimuli according to the task context framed from exemplars or from a verbal term. Therefore, the left rlPFC may be more involved in considering multiple relationships than in concept induction. This interpretation is supported by previous fMRI results (Wendelken et al., 2008) showing the involvement of the rlPFC in semantic analogy tasks both when participants were to retrieve the relationships between pairs of words (such as "painter : brush") and when a relational term (such as "uses") was explicitly given. Reinforcing this hypothesis, according to patient studies, prefrontal damage may cause an impairment in analyzing multiple relationships similar to those employed here (Krawczyk et al. 2008). Previous studies have demonstrated that the left rlPFC is involved in analogy tasks whatever the nature of stimuli used (i.e. visuospatial, verbal or semantic), or the type of analogy schema (mathematical, logical, geometrical, or semantic relation) (Vartanian et al. 2012). The current results reinforce this idea as the use of various stimuli and heterogeneous analogy schemata in our Analogy tasks suggests that the left rlPFC involvement in analogy is not schema-specific. Thus, the current findings add to the existing evidence for a role of the left rlPFC in domain-general relational integration (Christoff et al., 2001; Reynolds et al. 2006) and

more importantly demonstrate that inter-individual variability in relational reasoning can be supported by structural variation within the left rlPFC.

The rlPFC has been associated with a variety of other cognitive functions and complex cognitive abilities (for reviews see Dumontheil et al. 2008; Ramnani and Owen, 2004) that require the integration of distinct elements of information, such as coordinating goals with subgoals and multitasking (Burgess et al. 2007; Roca et al. 2011), switching attention to stimulus-oriented or stimulus-independent thoughts (Raichle et al. 2001; Gilbert et al. 2005; Burgess et al. 2007), creativity tasks (Gonen-Yaacovi et al. 2013) and fluid intelligence (Geake and Hansen 2005). Whether the rlPFC supports common relational integration processes required by these diverse functions or whether distinct rlPFC subregions have distinct roles in these processes remains to be determined. Exploring the anatomical connections of the rlPFC, an integrative region, may shed some light on this question.

Tractography performed in the current study revealed that the left rlPFC is connected with the semantic system, the ventral visual stream and language areas (temporal and posterior parietal regions) via the AF, IFOF, and UF. It is also connected with the contralateral rostral PFC via callosum fibers and with the thalamus via the anterior thalamic radiations. These connections may enable the integration of the relations among perceived stimuli and the conceptual schema that is either inferred from exemplars (in the AnalogyFind condition) or verbally processed based on the relational term displayed (AnalogyApply).

Role of temporal areas in analogy

The current VBM study also revealed a bilateral anterior and inferolateral temporal region for analogy that has not been reported in previous functional MRI studies but has been related to analogical reasoning deficits in patients with temporal damage (Morrison et al. 2004). In functional MRI, the anterior temporal lobe (ATL) has been rarely reported in association with relational reasoning, partly because this region is often not acquired with MRI or is too sensitive to distortion artifacts caused by magnetic susceptibility, as has been suggested by semantic memory studies (Visser et al. 2010). When reported, the ATL was associated with semantic distance between analogs (Green et al., 2010) or with lower activity during relational reasoning compared with control tasks (Wendelken et al. 2008; Geake and Hansen 2010; Volle et al. 2010). With VBM methods, the ATL region has been found to correlate with relational reasoning measured by the Raven matrices test (Yuan et al. 2012), which is consistent with our analogy results.

The bilateral ATL is thought to support semantic and/or abstract representations (Hodges et al. 1992; Rogers et al. 2006; Hodges and Patterson 2007; Gorno-Tempini et al 2011) and has been proposed to serve as an amodal (or transmodal) and domain-general semantic "hub," linking different aspects of knowledge distributed in other brain regions (Patterson et al. 2007; Jefferies 2013). This hypothesis is supported by structural imaging studies in patients with temporal damage (Lambon Ralph et al. 2010, 2012), functional imaging investigations (Vigneau et al. 2006; Binder et al. 2009; Binney et al. 2010; Visser et al. 2010), morphometry (de Zubicaray et al. 2011) and transcranial magnetic stimulation (TMS) studies (Pobric et al. 2009, 2010), all showing a critical role of the ATL in category-general semantic tasks. Some of these results especially involved inferolateral ATL subregions very close to our analogy region (Figure S3). Although our Analogy task used symbols, it is possible that analogical reasoning is

fundamentally embedded in the semantic network. This would suggest that concepts stored in the semantic network are necessary to understand any type of analogy, even between symbols, as suggested previously (Knowlton et al. 2012) and may even be verbally formulated (see Volle et al. 2010). Our analogy tasks used various conceptual relations or schemas, which is consistent with the role of the ATL region in semantic memory and in abstracting away from surface similarities (Patterson et al. 2007; Pobric et al. 2010). It is also possible that the left and right ATL reflect verbally and perceptually encoded conceptual representations respectively as our tasks did not allow this distinction (Acres et al. 2009; Gainotti 2012; 2014; Mesulam et al. 2013; Gil-Robles et al. 2013).

The distinct brain correlates of our Analogy and Match tasks suggest a functional dissociation between their neural correlates, with abstract analogies being associated with an inferolateral portion bilaterally and visual similarity with a posterior region and a more medial portion of the right ATL in the fusiform gyrus. The right dominance of the brain correlates of the visual matching task is consistent with the hypothesis of a right inferotemporal advantage for the processing of visual information, while the left temporal cortex may process verbal information (Coello et al. 2013; Gainotti 2014). The fusiform gyrus is part of the ventral stream of visual information processing and allows for the identification of items (Tyler et al. 2013). Visual features had to be matched based on similarity in the Match tasks, which could explain the involvement of this region in the Match tasks.

In the right ATL region, brain correlates of Analogy tasks were more lateral to those of the Match tasks. Anatomical-functional distinctions have been described in the left ATL region (Pascual et al. 2013; Mesulam et al. 2013; Gil-Robles et al. 2013) wherein the inferolateral part is connected to the semantic and default network functionally (Pascual et al. 2013) and

anatomically (Fan et al. 2013) and a more ventral and medial region within the fusiform gyrus is connected to visual networks. Consistent with this functional specialization, our tractography results showed a distinct anatomical connectivity between the inferomedial and the inferolateral right ATL in addition to their functional orientation toward Analogy and Match performance. One important difference between the anatomical connectivity patterns of the temporal regions associated with Analogy and Match performance was that only the inferolateral analogy regions (lTEMP and rTEMP) were connected to the AF.

The tractography results also showed that the rostral frontal and temporal Analogy regions shared the AF, which connected the left rlPFC (lPOL) and the left inferolateral ATL (lTEMP) regions. AF projections extend beyond the classical Broca-Wernicke model (Thiebaut de Schotten et al. 2012), and AF functions have recently been extended beyond classical language models including verbal working memory or the ability to learn new "words" (Catani et al. 2007; Dick and Tremblay 2012; López-Barroso et al. 2013). It is therefore likely that rlPFC and ATL regions exchange information about the relational concept evoked in Analogy tasks, although semantic memory is classically associated with UF or IFOF (Duffau et al. 2005, 2008; de Zubicaray et al. 2011). Finally, we cannot exclude that the rlPFC and ATL regions may also be indirectly connected anatomically or that these connections are not involved in analogical reasoning. Overall, the role of AF in analogical reasoning and how the rlPFC and ATL regions are part of a functional network subserving analogies (de Zubicaray et al. 2011; Wei et al. 2012; Fan et al. 2013; Pascual et al. 2013) will need further specific exploration.

Rule induction is related to a more posterior PFC region

Our findings also suggest that separate analogy components are associated with distinct lateral prefrontal regions. Whereas reasoning based on relationships rather than on the stimuli themselves is associated with the left rlPFC (lPOL), finding the matching rule or schema is related to the morphology of a more posterior prefrontal region (lmidPFC), whether the rule is concrete (same features) or more abstract (in analogy). This later result is consistent with the role of the lateral left PFC in inductive reasoning demonstrated by lesion studies (Reverberi et al. 2005a; 2005b) and functional neuroimaging (Goel and Dolan 2004; Crescentini et al. 2001; Jia et al. 2011; Liang et al. 2014). Studies contrasting rule identification (find the rule) and rule following (apply a given rule) have reported activity in a left lateral prefrontal area very close to our lmidPFC region (Crescentini et al. 2001; Jia et al. 2011). The role of this region in inductive reasoning has been related to its role in detecting regularities across stimuli and generating hypotheses from them (Crescentini et al. 2011). Our paradigm did not allow to clarify the precise cognitive and executive operations supported by the midPFC and engaged in our tasks, and more generally in rule induction. Patient studies also have shown that the left lateral prefrontal cortex is critical for rule finding more than for rule following (Reverberi et al. 2005a, b), suggesting that this region is especially important for inductive reasoning and that the consequences of its damage should be assessed in clinical practice.

Taken together, these findings suggest that distinct brain regions support distinct analogy processes: the left rlPFC may support the processing and integration of the relationships between stimuli enabling the representation of a conceptual schema in interaction with the ATL regions involved in semantic memory. A more posterior lateral PFC region may be engaged in the inference processes required to identify a matching rule in exemplar-based conditions, whether the rule is concrete (a perceptual match) or more abstract (an analogy schema). The two distinct

prefrontal regions we observed may also be linked to the recent models describing a caudal-rostral organization of prefrontal cortex according to distinct levels and types of abstraction (Badre 2008 for a review), in which most anterior prefrontal regions support more abstract rules or action representations or complex relational/semantic integration (Green et al. 2006) than more posterior ones.

Interpretation of correlations with brain structures

We observed negative correlations between local GM volume and performance in both the Analogy and Match conditions. In other non-frontal regions, we also observed positive correlations. In both cases, these regions were found to be activated in functional imaging studies using related tasks or processes. The common notion of "the more brain volume the better" appears to need reconsideration, at least in some cerebral regions. While some of the evidence does suggest that greater local GM volume is associated with better performance, especially when comparing patients to controls or after a specific training or acquired expertise (Maguire et al. 2000; Draganski and May 2008; Takeuchi et al. 2010, 2011, 2013), others report better performance associated with less local GM volume, especially in the prefrontal regions (Moore et al. 2009; Buda et al. 2011; Goh et al. 2011; Smolker et al. 2014). Several studies also showed both positive and negative correlations for different brain regions and different aspects of multi-faceted concepts, such as empathy (Banissy et al. 2012), intelligence (Frangou et al. 2004), or creativity (Jung et al., 2010). Overall, it appears that the observation of positive or negative structure-task correlations depends heavily on brain regions, on the population studied, and on the particular process assessed. Thus, it is important to consider why less GM signal in VBM

would actually facilitate performance. A first possibility may be that less GM volume allows greater WM volume (i.e., less cell bodies and more connections; Paus 2005; Goh et al. 2011). This may be especially relevant for rostral PFC, where dendritic neuropil is more developed than in other comparable areas of the cortex while the density of cell bodies is low, pointing to its high integrative properties (Ramnani and Owen 2004; Dumontheil et al. 2008). Alternatively, the process of synaptic pruning that occurs during brain maturation and leads to frontal cortex thinning (Dumontheil et al. 2008; Shaw et al. 2006) has also been associated with an improvement in executive functions (Kharitonova and Munakata 2011). Cortical thickness has been specifically measured in an analogy study on adolescents (Krawczyk et al., 2010b) that demonstrated a correlation between rlPFC thinning and a better performance in analogical reasoning. This study pointed to a more medial rlPFC region than the current results, likely be due to a difference in the material used, i.e. meaningful pictures with distinct difficulty levels. These findings reinforce the hypothesis that brain development that leads to a thinner left rlPFC may confer higher analogical abilities. Differences in local brain development may also explain variations observed in the left rlPFC involvement in analogy tasks during childhood (Dumontheil et al. 2010). In this context, although the significance of "macroscopic" anatomical variations is not yet understood in terms of microscopic variability (such as cellular or synaptic variability), possible interpretations of our data are that good performers may have experienced a more efficient synaptic pruning or cortical myelination, leading to a thinner rostral PFC cortex.

Our findings show that the macroscopic correlates of cognitive abilities are not homogeneous across regions, suggesting that the mechanisms supporting the cognitive capacities of the cortex may be distinct in the frontal and temporal regions. These mechanisms may rely differently on cellular or neuropil changes, or on surface folding or cortical thickening (Mechelli

et al. 2005), and may be related to both genetic and environmental factors. A better understanding of the physiological bases of local increases and decreases in GM volume will be necessary to interpret our VBM results (Kanai and Rees 2011; Eriksson et al. 2009). It is noteworthy that in functional MRI, the biological significance of activation and deactivation is not fully understood either (Logothetis 2008).

As the performances in our Analogy and control Match tasks were not equivalent, we can not exclude that the difference in their cerebral correlates could be related to difficulty-related processing. However, we believe that the brain correlates of our Analogy tasks reflect analogical reasoning abilities, because our findings are consistent with previous studies that controlled difficulty levels (Hampshire et al. 2011; Kroger et al. 2002; Cho et al. 2010) or equated performance between analogy and control tasks (Watson et al. 2012; Krawczyk et al. 2010a). Activation within the same rlPFC region has been consistently reported during tasks that involve analogical reasoning whatever the difficulty or perceptual nature of the material used (see a meta-analysis from Vartanian et al. 2012). Furthermore, in a previous study (Wartenburger et al. 2009) the left rlPFC was only moderately modulated by difficulty in analogical reasoning.

Finally, despite the large age range of the participants, it is unlikely that aging may have biased the results for several reasons. First, our analyses were corrected for age and total GM volume. Second, the correlation between GM volume and age within the left rlPFC region (lPOL) disappeared when controlling for the total GM volume, which does not argue for a local effect of ageing on the GM volume of the rlPFC.

Conclusion

The originality of this study was to investigate the structural correlates of analogical reasoning using VBM coupled with an anatomical connectivity study. Combined with previous functional imaging reports, our results suggest that the left rlPFC and inferolateral ATL support cognitive processes engaged when solving analogies and that variability in their anatomy predicts individual differences in the efficiency of this processing. Considering previous reports, the profile of the brain correlates observed in our distinct experimental conditions suggests that variability in the left rlPFC structure and the temporal semantic regions may reflect an ability to process multiple relationships between stimuli and to link them to a conceptual schema. The ability to infer the analogy schema from exemplars may depend on a more posterior left lateral PFC region. Further research would be necessary to deepen our understanding of the roles these regions play in reasoning processes and their relationship to recent models of prefrontal organization, to clarify how they interact via their anatomical or functional connectivity, and to examine how damage to these areas or their connections provokes an impairment in analogy abilities. Other methods that allow stronger causality, such as lesion studies or TMS, would allow for drawing more definitive conclusions about the involvement of the left rlPFC in reasoning. The very few existing pioneering studies in this direction indeed highlighted the importance of an intact PFC for relational reasoning (Boroojerdi et al. 2001; Morrison et al. 2004; Krawczyk et al. 2008; Schmidt et al. 2012). The current findings offer new anatomical targets for future research on the cognitive consequences of damage to these regions and their connections.

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Tables

Table 1. VBM whole-brain analysis showed positive GM correlations with mean accuracy in Analogy, Match, Find and Apply conditions. Whole-brain analysis on GM volume was conducted to investigate significant results at $p < .001$ uncorrected for multiple comparisons with a minimal cluster size of 100 voxels. All significant positive correlations are reported for each condition with their associated brain regions and BA. The MNI coordinates, *P* (unc.), *T* values, and cluster size are reported. aITG = Anterior and Inferolateral part of the Inferior Temporal gyrus; NS: non significant.

Condition	Brain region	BA	MNI coordinates			*P* (unc.)	*T* value	Cluster size	Label
			x	y	z				
Analogy	aITG	20	46	3	-36	<.001	4.25	573	rTEMP
	aITG	20	-52	-9	-26	<.001	4.43	175	lTEMP
Match	NS								
Find	NS								
Apply	NS								

Table 2. VBM whole-brain analysis showed negative GM correlations with mean accuracy in Analogy, Match, Find and Apply conditions. Whole-brain analysis on GM volume was conducted to investigate significant results at $p < .001$ uncorrected for multiple comparisons with a minimal cluster size of 100 voxels. All significant negative correlations are reported for each condition with their associated brain regions and BA. The MNI coordinates, *P* (unc.), *T* values, and cluster size are reported. MFG = Middle Frontal Gyrus; aFG = Anterior part of the Fusiform Gyrus; IFS: Inferior Frontal sulcus IPL= Inferior Parietal lobule; ITG: Inferior Temporal Gyrus; rlPFC = rostrolateral prefrontal cortex. NS: non significant.

Task	Brain region	BA	MNI coordinates			*P* (unc.)	*T* value	Cluster size	Label
			x	y	z				
Analogy	rlPFC (MFG)	10/46	-40	53	1	< .001	4.097	173	lPOL
Match	aFG	20	30	-1	-38	< .001	4.07	165	rTEMPmatch
	ITG	20	51	-15	-35	< .001	3.75	105	
	IPL	2	-46	-28	43	< .001	4.13	221	
Find	IFS	45	-39	38	16	<.001	4.27	120	lPFC
Apply	NS	-	-	-	-	-	-	-	-

Table 3. Linear regression analyses between significant VBM clusters and each experimental condition. In each model, age, genre, education, total GM volume were entered as covariates of non-interest.

Dependant variable:	Predictor: AnalogyApply,	Predictors: AnalogyFind,	Predictors MatchApply	Predictors MatchFind
lPOL volume	F(5,48) = 5.890, $p < .001$, accounted for approximately 32% of the variance lPOL volume was predicted by AnalogyApply score (Beta = -.425, ***p* = .003**) and to a less extent by age (Beta = -.387, $p = .028$)	F(5,48) = 5.40, $p = .001$, accounted for approximately 30% of the variance lPOL volume was predicted by AnalogyFind score (Beta = -.392, ***p* = .006**) and to a less extent by age (Beta = -.412, $p = .023$)	F(5,48) = 3.278, $p = .013$, accounted for approximately 18% of the variance lPOL volume was not significantly predicted by MatchApply score (Beta = -.066, $p = .613$) nor by age, gender, education or total GM volume	F(5,48) = 3.255, $p = .013$, accounted for approximately 17.5% of the variance lPOL volume was not significantly predicted by MatchFind score (Beta = -.054, $p = .680$) nor by age, gender, education or total GM volume
rTEMP volume	F(5,48) = 2.283, $p = .061$, accounted for approximately 11% of the variance rTEMP volume was predicted by AnalogyApply score only (Beta = .256, ***p* = .024**)	F(5,48) = 3.748, $p = .006$, accounted for approximately 21% of the variance rTEMP volume was predicted by AnalogyFind score only (Beta = .503**, *p* = .001**)	F(5,48) = 1.079, $p = .384$, accounted for approximately 1% of the variance rTEMP volume was not predicted by MatchApply score (Beta < .001, $p = .998$) nor by age, gender, education or total GM volume	F(5,48) = 1.009, $p = .378$, accounted for approximately 1% of the variance rTEMP volume was not predicted by MatchFind score (Beta = .031, $p = .831$) nor by age, gender, education or total GM volume
lmidPFC volume	F(5,48) = 9.207, $p < .001$, accounted for approximately 44% of the	F(5,48) = 13.393, $p < .001$, accounted for approximately 54% of the	F(5,48) = 8.159, $p < .001$, accounted for approximately 40% of the variance	F(5,48) = 11.569, $p < .001$, accounted for approximately 50% of the

	variance lmidPFC volume was predicted by age (Beta = -.506, *p* = .002) but not by AnalogyApply score (Beta = -.205, *p* = .098)	variance lmidPFC volume was predicted by AnalogyFind score (Beta = -.416, ***p* < .001**), by age (Beta = -.564, p < .001) and to a less exetent by total GM volume (Beta = .329, *p* = .023)	lmidPFC volume was predicted by age (Beta = -.480, *p* = 0.004) but not by MatchApply score (Beta = -.012, *p* = .912)	variance lmidPFC volume was predicted by AnalogyFind score (Beta = -.307, ***p* = .004**), by age (Beta = -.527, *p* = .001)
rTEMPmatch volume	F(5,48) = 1.080, *p* = .383, accounted for approximately 1% of the variance rTEMPmatch volume was not predicted by AnalogyApply score (Beta = -.005, *p* = .974)	F(5,48) = 1.167, *p* = .339, accounted for approximately 1.5% of the variance rTEMPmatch volume was not predicted by AnalogyFind score (Beta = .101, *p* = .535) nor by age, gender, education or total GM volume	F(5,48) = 2.218, *p* = .068, accounted for approximately 10% of the variance rTEMPmatch volume was predicted by MatchApply score (Beta = -.306, ***p* = .028**) and gender (Beta = -.303, *p* = .033)	F(5,48) = 1.981, *p* = .098, accounted for approximately 8.5% of the variance rTEMPmatch volume was predicted by MatchFind score (Beta = -.275, ***p* = .050**) and gender (Beta = -.305, *p* = .034)

Table 4. SVC analysis: ROI analysis (p < .05 corrected based on Family-wise Error) examining the negative correlation between GM volume in *a priori* defined rlPFC regions (defined from fMRI) and accuracy in tasks conditions (in percent of correct responses). Cluster size, T values, fwe-corrected P values, and cluster size are provided. rlPFC = rostrolateral prefrontal cortex.

ROI	MNI coordinates (x, y, z)			Condition	*p* (fwe)	T value	Cluster size
left rlPFC	-44	50	-4	Mean Analogy	0.003	4.09	189
				Mean Find	ns	-	-
				AnalogyApply	0.013	3.54	160
				AnalogyFind	0.020	3.35	77
				MatchApply	ns	-	-
				MatchFind	ns	-	-
right rlPFC	+44	50	-4	Mean Analogy	ns	-	-
				Mean Find	ns	-	-
				AnalogyApply	ns	-	-
				AnalogyFind	ns	-	-
				MatchApply	ns	-	-
				MatchFind	ns	-	-

Figure captions

Figure 1: A trial for each condition differentiating between Apply and Find conditions in the Analogy and Match tasks. In each condition, participants were asked to choose from the sets of stimuli on the right (target sets) the one that matched the left set of stimuli (source set) according to four distinct conditions. In the AnalogyApply condition (bottom left), participants had to apply a given analogical relationship to the sets to determine the correct target (here, the relationship consisted of a mirror image between the left and right stimuli (letter "g") of the source set); the correct response is the bottom right target set), while in the AnalogyFind condition (top left), the relationship had to be found by the participant (here, the relationship is an increase in lightness of the stimuli in the source set; the correct response is the top right target set). In the MatchApply condition (bottom right), participants had to apply a matching rule based on a given perceptual feature between the source and correct target set (in the displayed example, the matching feature is colors, and the correct answer is the top right target set), while in the MatchFind condition (top right), they had to find the matching rule, i.e. the perceptual feature shared between the sets (in the displayed example, the left source set and the top right target set share a common number of stimuli).

All of the displayed examples consist of intradimension analogies. However, the analogy task included both intradimension and cross-dimension analogies, as described in Volle et al. 2010 and illustrated in supplementary Figure S1.

Figure 2. Mean Accuracy (in % of correct responses) and reaction times (RT in ms) of each condition. Overall, participants were significantly more accurate and responded faster in the Match conditions compared to the Analogy conditions. Error bars indicate standard deviations; ** indicates the significant difference in accuracy and in RTs between Analogy mean and Match mean conditions.

Figure 3. Results from the VBM analyses.

Significant regions associated with variations in GM volume related to performance are superimposed on an anterolateral view (top left) and anteroinferior view (top right) of a brain rendering. The VBM whole-brain analyses identified a left rlPFC region ("lPOL", in red), in which GM volume negatively correlated with mean performance on Analogy tasks, a left and right anterolateral temporal region (in green), in which GM volume positively correlated with mean performance on Analogy tasks, a left caudal prefrontal region ("lmidPFC", purple), in which GM volume negatively correlated with mean performance on Find trials, and a right anteromedial temporal region ("rTEMPmatch", in blue), in which GM volume negatively correlated with mean performance on Match tasks.

GM measures were extracted from each individual VBM preprocessed images and averaged across voxels within these 4 significant clusters evidenced in the whole-brain analyses. Performance on each experimental condition was entered as a dependent variable and GM volume in each region as an independent variable in separate multiple regression models, in which age, gender, education and total GM volume were covaried out.

Plots between performance on each experimental condition and GM measures within these four regions are displayed: the left rlPFC region ('lPOL', in red), the left lateral PFC region ('lmidPFC', in purple), the right anterolateral temporal region ('rTEMP, in green), and an anteromedial temporal region ("rTEMPmatch", in blue). X axes represent the residuals of accuracy in each experimental condition (AnalogyApply, AnalogyFind, MatchApply, Match Find) and Y axes the residuals of the mean GM volume within each region (lPOL, lmidPFC, rTEMP, rTEMPmatch).

Figure 4. Connectome of the left rlPFC region (lPOL), left and right ATL (lTEMP and rTEMP), rTEMPmatch, and lmidPFC region. Tracts of lPOL (in red), r/lTEMP (in green), rTEMPmatch (in blue), and lmidPFC (in purple) are superimposed on a transparent brain rendering (left side) and on axial slices showing their anatomical connectivity (right side). The upper part of the figures shows the overlap of lPOL and lTEMP tracts on the arcuate fasciculus. The inferior part of the figure shows that rTEMP and rTEMPmatch tracts poorly overlap on the ILF, and that lmidPFC has mainly intra-frontal connections. ATR: anterior thalamic radiations; FMT: Frontomarginal fasciculus; IFOF: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; FIL: Frontal inferior longitudinal fasciculus.

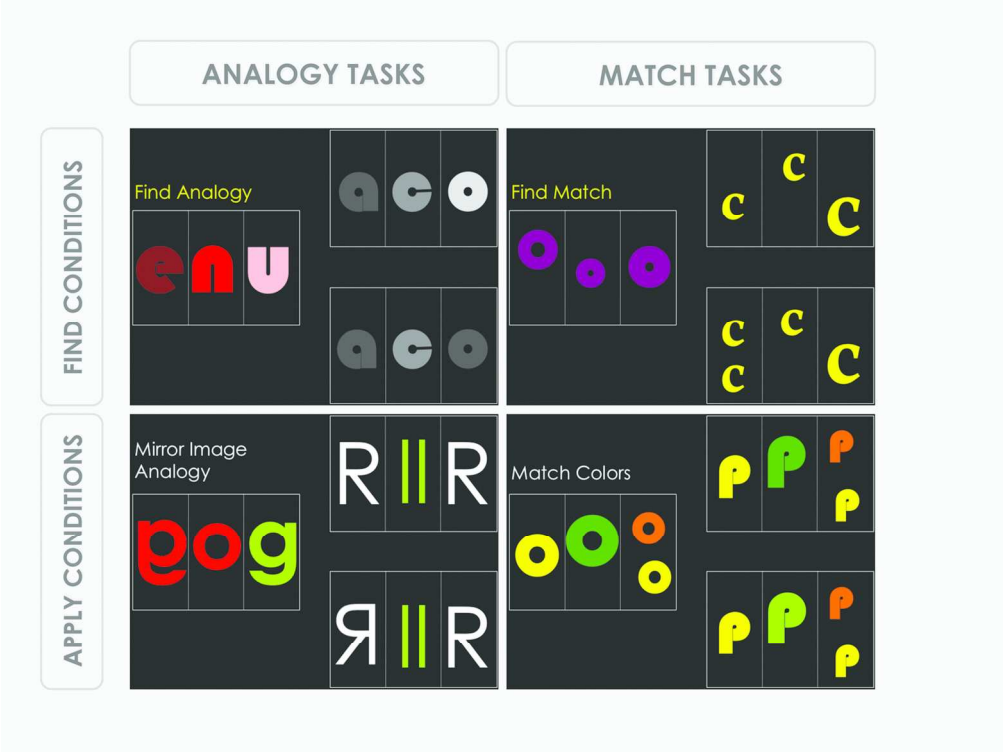

Figure 1. A trial for each condition differentiating between Apply and Find conditions in the Analogy and Match tasks. In each condition, participants were asked to choose from the sets of stimuli on the right (target sets) the one that matched the left set of stimuli (source set) according to four distinct conditions. In the AnalogyApply condition (bottom left), participants had to apply a given analogical relationship to the sets to determine the correct target (here, the relationship consisted of a mirror image between the left and right stimuli (letter "g") of the source set); the correct response is the bottom right target set), while in the AnalogyFind condition (top left), the relationship had to be found by the participant (here, the relationship is an increase in lightness of the stimuli in the source set; the correct response is the top right target set). In the MatchApply condition (bottom right), participants had to apply a matching rule based on a given perceptual feature between the source and correct target set (in the displayed example, the matching feature is colors, and the correct answer is the top right target set), while in the MatchFind condition (top right), they had to find the matching rule, i.e. the perceptual feature shared between the sets (in the displayed example, the left source set and the top right target set share a common number of stimuli). All of the displayed examples consist of intradimension analogies. However, the analogy task included both intradimension and cross-dimension analogies, as described in Volle et al. 2010 and illustrated in supplementary Figure S1.

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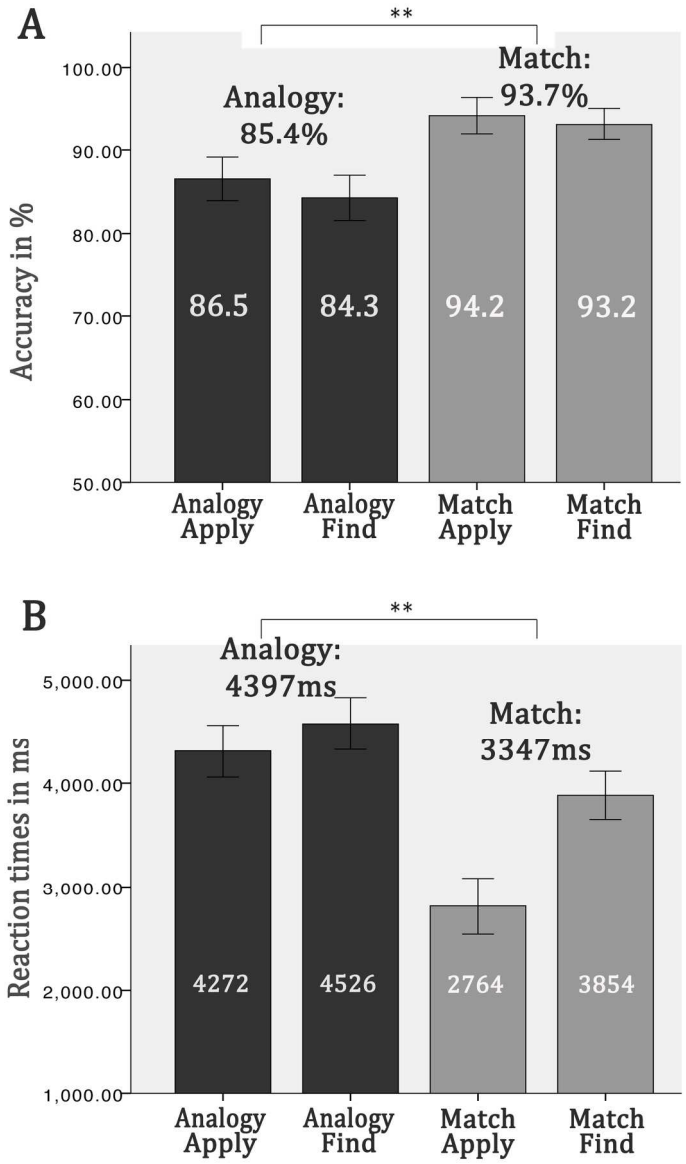

Figure 2. Mean Accuracy (Acc in % of correct responses) and reaction times (RT in ms) of each condition. Overall, participants were significantly more accurate in the Match conditions compared to the Analogy conditions and responded faster in the Match conditions compared to the Analogy conditions. Error bars indicate standard deviations; ** indicates the significant difference in accuracy and in RTs between Analogy mean and Match mean conditions.
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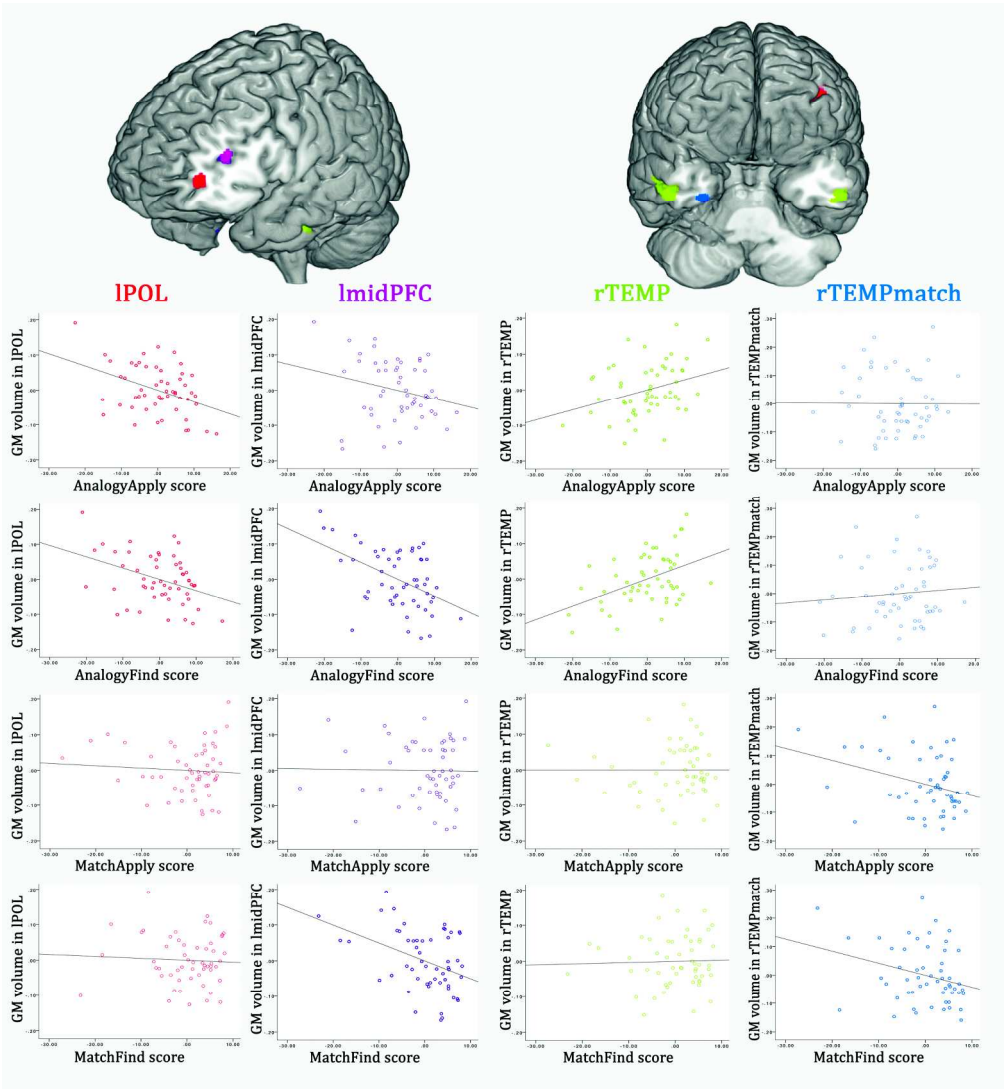

Figure 3. Results from the whole-brain VBM analysis.

Significant regions associated with changes in GM volume related to performance are superimposed on an anterolateral view (left) and anteroinferior view (right) of a brain rendering. The VBM whole-brain analyses identified a left rlPFC region ("lPOL", in red), in which GM volume negatively correlated with mean performance on Analogy tasks, a left and right anterolateral temporal region (in green), in which GM volume positively correlated with mean performance on Analogy tasks, a left caudal prefrontal region ("lmidPFC", purple), in which GM volume negatively correlated with mean performance on Find trials, and a right anteromedial temporal region ("rTEMPmatch", in blue), in which GM volume negatively correlated with mean performance on Match tasks.

GM measures were extracted from each individual VBM preprocessed images and averaged across voxels within the significant clusters evidenced in the whole-brain analysis. Performance on each experimental condition was entered as a dependent variable and GM volume in these four regions as an independent variable in separate multiple regression models, in which age, gender, education and total GM volume were covaried out.

Plots between performance on each experimental condition and GM measures within these four regions are displayed: the left rlPFC region ('lPOL', in red), the left lateral PFC region ('lPFC', in purple), the right anterolateral temporal region ('rTEMP, in green), and an anteromedial temporal region ("rTEMPmatch", in

blue). X axes represent the residuals of accuracy in each experimental condition (AnalogyApply, AnalogyFind , MatchApply, Match Find) and Y axes the residuals of the mean GM volume within each cluster observed in the whole-brain analysis (lPOL, lmidPFC, rTEMP, rTEMPmatch).

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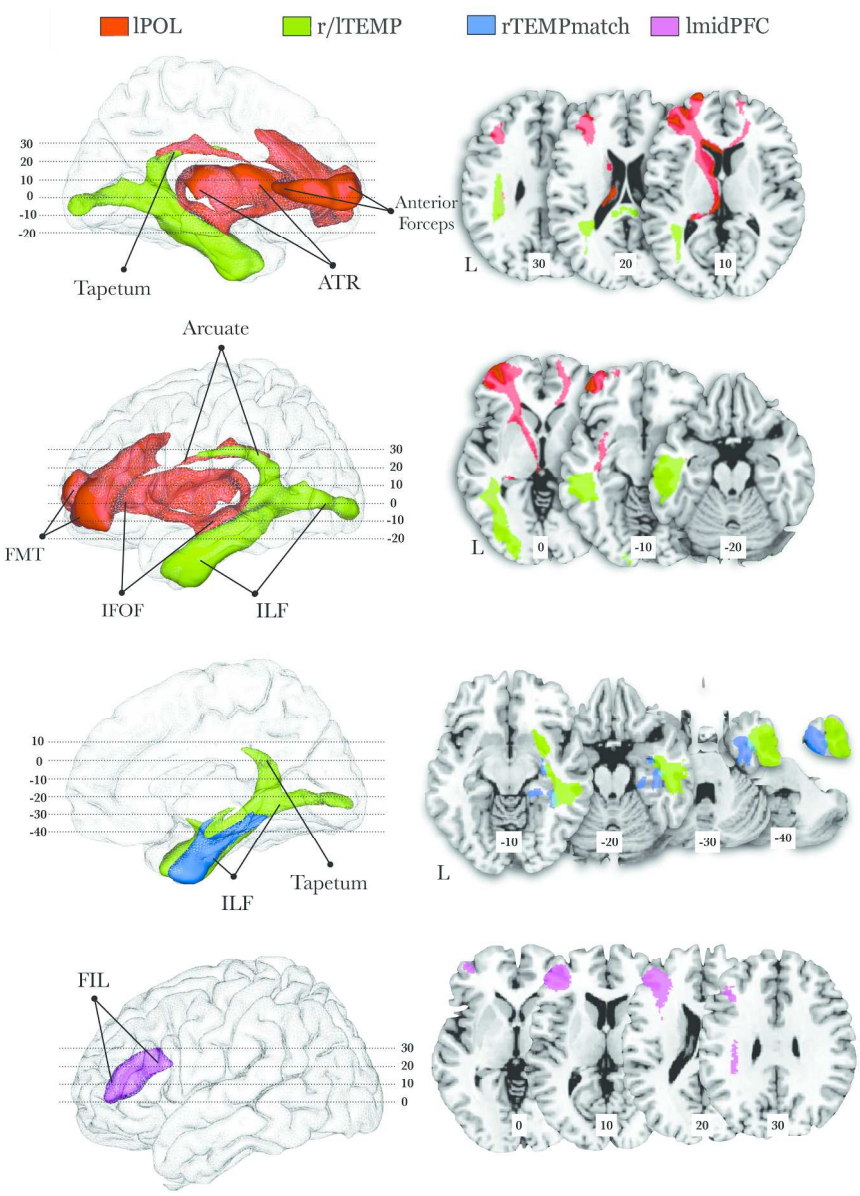

Figure 4. Connectome of the left rlPFC region (lPOL) left and right ATL (lTEMP and rTEMP) and lmidPFC region. Tracts of lPOL (in red), r/lTEMP (in green) and lmidPFC (in purple) are superimposed on a transparent brain rendering (left side) and on axial slices of the anatomical connectivity (right side). The upper part of the figures shows the overlap of lPOL and lTEMP tracts on the arcuate fasciculus. rTEMP and rTEMPMATCH tracts poorly overlap on the ILF. lmidPFC had mainly intrafrontal connections. ATR: anterior thalamic radiations; FMT: Frontomarginal fasciculus; IFOF: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; FIL: Frontal inferior longitudinal fasciculus.
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Supplementary figure S1: Example of intra- and cross-dimension analogy tasks using the same analogy schema "symmetry", and example of the match task.

Intra-dimension (left column) and cross-dimension (middle column) analogies used the same relational concepts. The figure displays examples of analogy trials using the schema "symmetry". In the intra-dimension task, the analogy concerned the same dimension in both the source and target sets (e.g., symmetry of the letter identity (top left), of colors (middle left) or the size (bottom left). In the cross-dimension task, the analogy concerned different dimensions (for instance, symmetry of size of the stimuli in the source and symmetry of color in the target stimuli – bottom of the middle column of the figure). The analogy schemas could also concern either the identity of figures, the number of stimuli, their lightness, or their texture. The features of the stimuli that were non relevant for the analogy schema (size, colors, identity, position, texture, or number) varied between source and target in order to avoid perceptual matching. In addition to "symmetry", there were 5 other different analogy schemas to discover in intra- and cross-dimension analogies, which were not used during the training. These schemas were either visuospatial or mathematical. They could be verbalized as ''progressive increase of a feature across the 3 stimuli in the set,'' ''mirror image,'' ''the first plus the second gives the third stimulus,'' ''the first minus the second gives the third stimulus,'' ''the last is a multiple of the first.''

In the Match task, there was one matching feature (i.e. letter identity of the stimuli (top right), identity of colors (middle right), or same size (bottom right) in the displayed trials, while the other features were distractors.

Supplementary figure S2: Comparison of the whole brain VBM results within rlPFC and peak maxima observed in previous fMRI studies.

Overlap of the current VBM result (whole-brain correlation between Analogy ability and GM volume in the left rlPFC, in red) with regions previously found associated with analogy in functional imaging (in cyan: activation maxima associated with analogy in Volle et al. (2010) fMRI study; in yellow: cluster Maxima observed in Vartanian's metaanalysis (2012) of analogical reasoning).

Supplementary figure S3: Comparison of the whole brain VBM results within ATL and peak maxima observed in previous functional imaging and TMS studies

Overlap of the current VBM result (whole-brain correlation between Analogy ability and GM volume in bilateral ATL, in green) with regions previously found associated with a semantic memory hub in TMS studies (Lambon Ralph et al 2009, in purple, coordinates -53, 4, -32 and 52, 2, -28). L: left side.

Example of intra- and cross-dimension analogy task using the same analogy schema "symmetry" and of match task.
Intradimension (left column) and cross-dimension (middle column) analogies used the same relational concepts. The figure displays examples of analogy trials using the schema "symmetry". In the intradimension task, the analogy concerned the same dimension in both the source and target sets (e.g., symetry of the letter identity (top left), of colors (middle left) or the size (bottom left). In the cross-dimension task, the analogy concerned different dimensions (for instance, symmetry of size of the stimuli in the source and symmetry of color in the target stimuli – bottom of the middle column of the figure). The analogy schemas could also concern either the identity of figures, the number of stimuli, their lightness, or their texture. The features of the stimuli that were non relevant for the analogy schema (size, colors, identity, position, texture, or number) varied between source and target in order to avoid perceptual matching. In addition to "symmetry", there were 5 other different analogy schemas to discover in intra- and cross-dimension analogies, which were not used during the training. These schemas were either visuospatial or mathematical. They could be verbalized as "progressive increase of a feature across the 3 stimuli in the set," "mirror image," "the first plus the second gives the third stimulus," "the first minus the second gives the third stimulus," "the last is a multiple of the first."
In the Match task, there was one matching feature (i.e. letter identity of the stimuli (top right), identity of colors (middle right), or same size (bottom right) in the displayed trials, while the other features were distractors.

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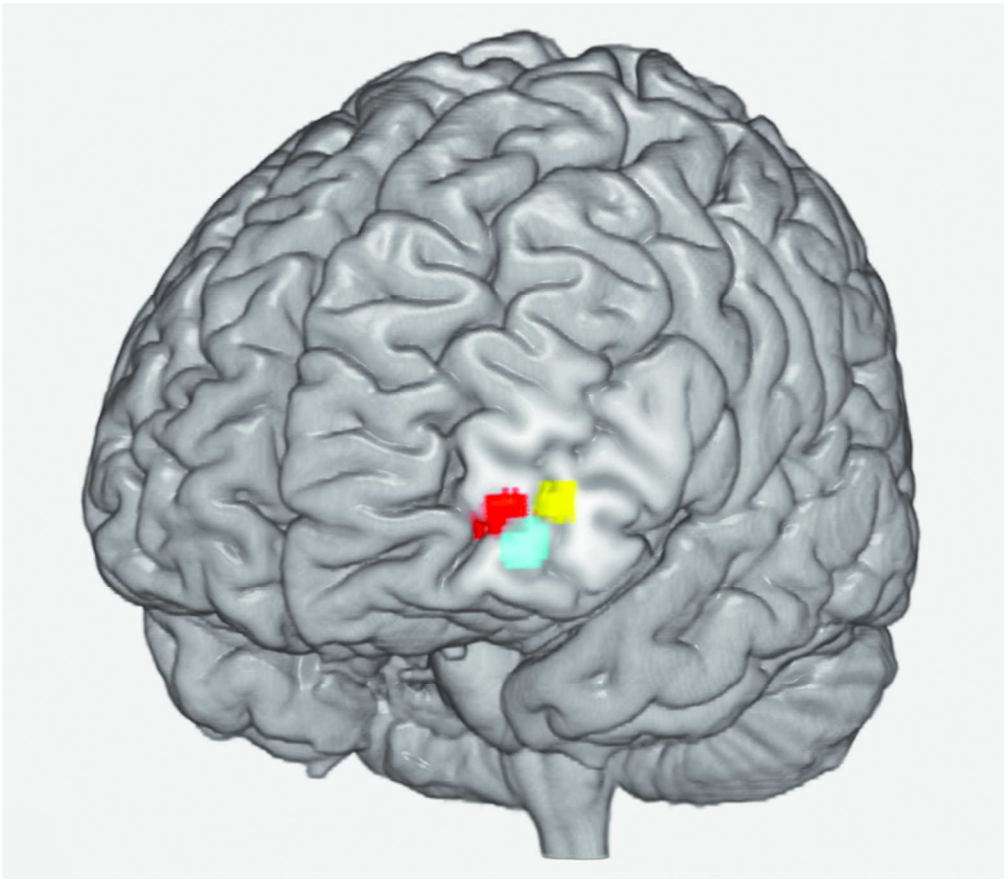

Comparison of the whole brain VBM results within rlPFC and peak maxima observed in previous results fMRI studies

Overlap of the current VBM whole brain correlation with Analogy ability and GM in the left rlPFC with previous regions found associated with analogy in functional imaging.
red: current VBM region showing a negative correlation to analogy in the whole-brain analysis; cyan: Activation maxima associated with analogy in Volle et al 2010 fMRI study; yellow: Cluster Maxima observed in Vartanian's metaanalysis (2012) of analogical reasoning.

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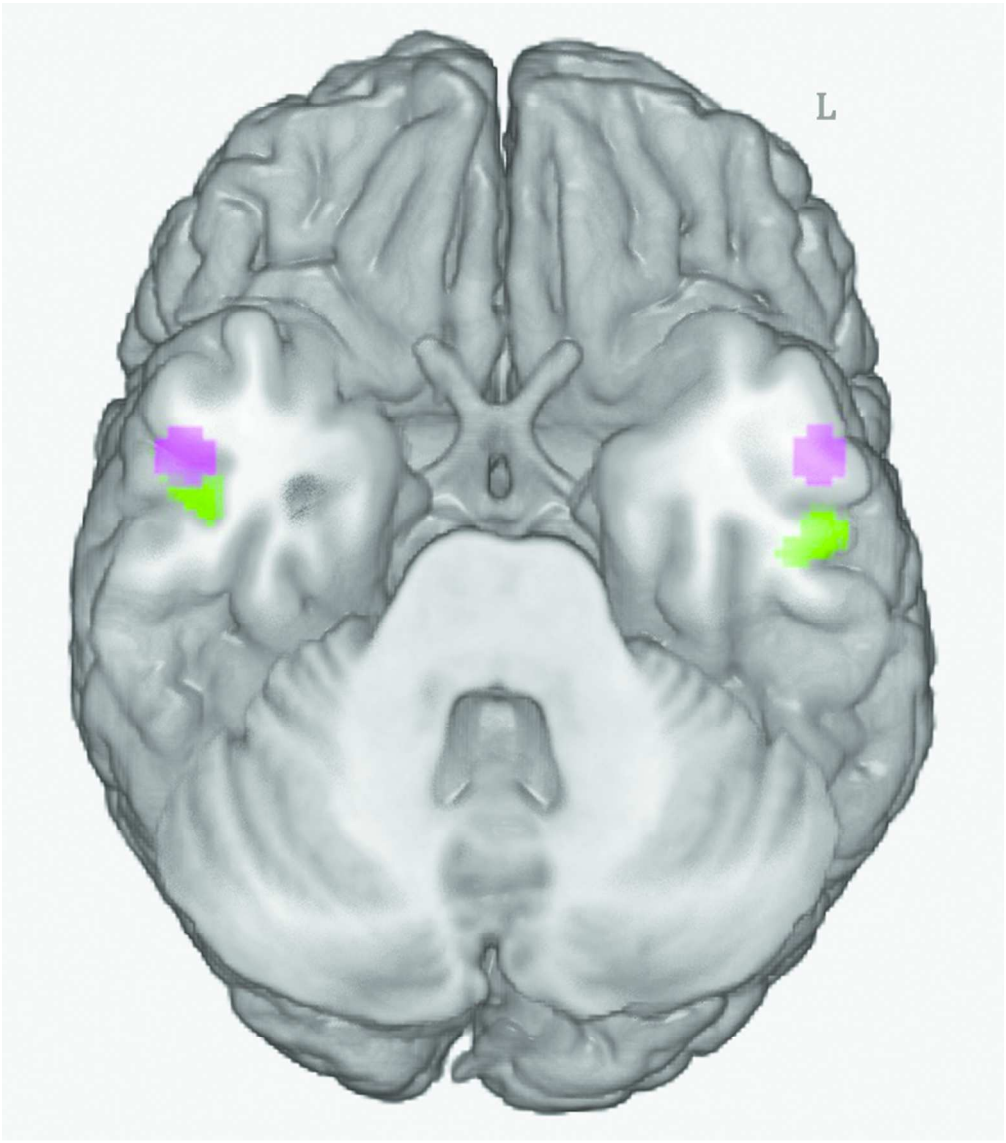

Comparison of the whole brain VBM results within ATL and peak maxima observed in previous results functional imaging and TMS studies
Overlap of the current VBM whole-brain correlation with Analogy ability and GM in the anterior temporal region with previous regions found associated with a semantic memory hub in TMS studies (Lambon Ralph et al 2009). Green: current VBM region showing a positive correlation with analogy in the whole-brain analysis; purple: Lambon Ralph 2009 sites of TMS stimulation evoking semantic deficits (coordinates -53, 4, -32 and 52, 2, -28). L: left side.

80x90mm (300 x 300 DPI)