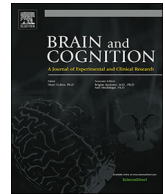




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Functional connectivity and the failure to retrieve meaning from shape in visual object agnosia

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ARTICLE INFO

Keywords:

Object recognition
fMRI
Functional connectivity
Lateral occipital cortex
Visual object agnosia

ABSTRACT

The neural mechanisms underlying the access to object knowledge from early representations of shape are little known. Functional imaging studies support the view that representations of visual properties are distributed across occipito-temporal cortex of both cerebral hemispheres. By contrast, brain lesion studies show that focal occipito-temporal damage may lead to object agnosia – a specific impairment of object recognition. How does distributed processing fit with functional specialization implied by the existence of stimulus-specific agnosias? Using fMRI we studied functional connectivity (FC) in a patient with object agnosia following left lateral occipital damage. Despite intact global and local processing of 2D and 3D object structure, the patient made consistent object identification errors. Seven experiments testing naming, visual matching or object priming showed that his errors mainly reflected the global shape similarity between objects. Compared to controls the patient exhibited strongly reduced FC between the damaged left and the intact right medial/lateral occipital cortex. In addition, controls showed stronger connectivity between the right occipital cortex and the left and right inferior and anterior temporal cortices. Interestingly, the patient also showed compensatory increases of FC between dorsal occipital and medial parietal cortex. These findings show that focal damage to the lateral occipital cortex may have global effects on representations of objects in bilateral occipito-temporal cortex, thus supporting the view that bilaterally distributed coding is necessary for the retrieval of associative knowledge from shape.

1. Introduction

A central topic of visual neuroscience deals with the neural mechanisms underlying the access to object knowledge from a 2D- or 3D-representation. Abundant neuroimaging studies support an organization of inferior and lateral occipito-temporal cortex into regions processing preferentially specific visual categories (for reviews, see Taylor & Downing, 2011; Ungerleider & Bell, 2011). For example, distinct activation maxima have been found for faces in the lateral fusiform and the inferior occipital gyrus (Kanwisher, McDermott, & Chun, 1997), objects in the lateral occipital cortex and posterior fusiform gyrus (Grill-Spector et al., 1999), tools in the medial fusiform gyrus (Chao, Haxby, & Martin, 1999), body parts in the posterior part of the inferior temporal gyrus (Downing, Jiang, Shuman, & Kanwisher, 2001) and words in the left fusiform area (Cohen et al., 2000). Some authors have taken these findings as evidence for a modular organization of the visual cortex,

according to which distinct occipito-temporal regions accommodate specialized mechanisms that deal with different classes of stimuli (Bell, Hadj-Bouziane, Frihauf, Tootell, & Ungerleider, 2009; Kanwisher, 2004; Taylor & Downing, 2011). The existence of patients with stimulus-specific agnosias following damage to discrete parts of occipito-temporal cortex lends support to this argument. For example, bilateral or right unilateral damage to the fusiform and lateral occipital cortex leads to prosopagnosia, a seemingly isolated deficit in processing and identifying faces (Rossion et al., 2003; Wada & Yamamoto, 2001). Focal damage to the left fusiform gyrus results in pure alexia, a selective deficit of reading characterized by a slow, letter-by-letter identification strategy (Gaillard et al., 2006; Pflugshaupt et al., 2009). Finally, bilateral or unilateral left occipito-temporal damage may produce a generalized impairment of object recognition. Such patients behave as if their perceptions were ‘stripped of’ their meaning (Anaki, Kaufman, Freedman, & Moscovitch, 2007; Farah, 2004; Grüsser & Landis, 1991;

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<https://doi.org/10.1016/j.bandc.2018.12.007>

Received 9 June 2018; Received in revised form 18 December 2018; Accepted 18 December 2018

Available online 25 December 2018

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Teuber, 1968): they are able to analyze visual properties to considerable detail (often enabling them to make accurate drawings of an object), make correct decisions regarding 2D or 3D object structure and may adequately match objects across changes of viewpoint, without any knowledge of their meaning or semantic category. Because of a supposed failure to access associative knowledge this kind of impairment has been termed visual associative agnosia or more generally, visual object agnosia (Albert, Reches, & Silverberg, 1975; Farah, 2004; Lissauer, 1890; Rubens & Benson, 1971).

Such findings might be interpreted as evidence that classes of visual objects are processed locally in circumscribed regions of visual cortex. However, when considering whole-brain modulations of activity it becomes clear that all visual stimuli evoke strongly distributed and overlapping activations across occipito-temporal cortex of both cerebral hemispheres (Haxby et al., 2001; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999). Most areas show a gradient of selectivity, rather than an all-or-none pattern of activity evoked by a specific stimulus class (Downing, Chan, Peelen, Dodds, & Kanwisher, 2006). Moreover, even the seemingly most specialized regions such as the ‘fusiform face area’ (Kanwisher et al., 1997) exhibit experience-dependent modulation of activity by stimuli belonging to other categories, such as cars or birds (Gauthier, Skudlarski, Gore, & Anderson, 2000; Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999). Similarly, though highly selective deficits in some rare patients seem to support a clear-cut dissociation between categories (Moscovitch, Winocur, & Behrmann, 1997; Rossion et al., 2003; Wada & Yamamoto, 2001) many show impairments for two or more categories (Farah, 1991; Martinaud et al., 2012). These findings suggest a non-local and widely distributed organization of visual processing across occipito-temporal cortex (Behrmann & Plaut, 2013; Haxby et al., 2001; Ishai et al., 1999). Together, they show that domain-specificity and distributed coding co-exist in the visual system, and thus have to be attributed for in cases of focal damage (Mahon & Caramazza, 2011).

On the other hand, if there is a high degree of distributed redundancy in higher-order representations, this should make the visual system relatively impervious to local damage. This is clearly not the case, as focal unilateral damage often suffices to cause severe agnosia for different kinds of visual stimuli. Thus, is the idea of distributed coding incompatible with the notion of functional specialization suggested by some cases of agnosia? A possible solution to this apparent contradiction is implied by the effects of focal brain damage on global network architecture. As shown by modeling and observational studies, local damage has distant effects on network structures within, as well as across hemispheres (Alstott, Breakspear, Hagmann, Cammoun, & Sporns, 2009; Gratton, Nomura, Perez, & D’Esposito, 2012). Such a mechanism could therefore principally explain the breakdown of performance following focal damage of a system that uses distributed coding. Two previous studies on patients with visual object agnosia have indeed shown that a focal occipito-temporal lesion may impact visual processing in the damaged and the preserved hemisphere. One patient showed a bilateral reduction of object-selectivity in the lateral occipital cortex following damage to the right posterior fusiform gyrus (Konen, Behrmann, Nishimura, & Kastner, 2011). Following left occipito-temporal damage another patient exhibited a complete bilateral breakdown of activity when viewing objects, while still showing significant activity to faces in his right hemisphere (Ptak, Lazeyras, Di Pietro, Schneider, & Simon, 2014). However, none of these studies focused on changes of functional connectivity (FC) as a possible physiological marker of diaschisis following local damage. We here show that impaired intra- and interhemispheric FC is indeed a neural marker of shape discrimination deficits after focal damage leading to visual object agnosia.

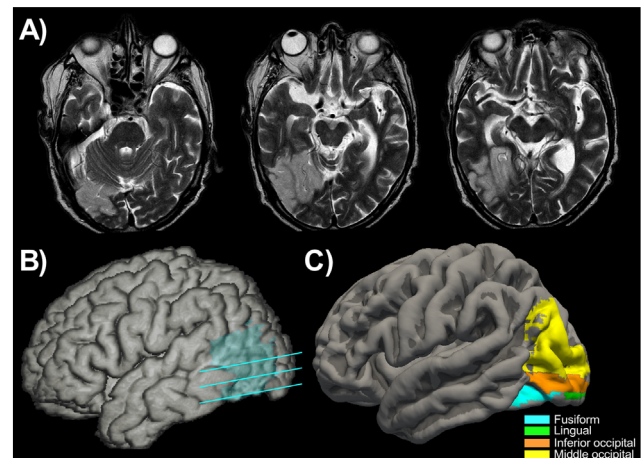


Fig. 1. Brain lesion of AL. (A) Axial MRI-images showing the patient’s left occipito-temporal ischemic brain lesion (note that the left hemisphere is shown on the left). (B) A normalized 3D-reconstruction of AL’s brain, his lateral occipital lesion emphasized in blue color. The parallel blue lines show approximate location of the three slices shown in A. (C) Lateral view of the template brain showing the four occipito-temporal areas defined as regions of interest for the connectivity analyses. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2. Materials and methods

2.1. Participants

The patient AL, who has visual object agnosia and pure alexia since he suffered a stroke of the left occipito-temporal region at the age of 72, and four age-matched healthy subjects (median age, 74 years) gave written consent to participate in this study. The study was approved by the Ethical committee of the University Hospital of Geneva.

AL’s cognitive deficits have been extensively documented in two previous studies focusing on his reading impairment (Di Pietro, Ptak, & Schneider, 2012) and object agnosia (Ptak et al., 2014), and will therefore only be summarized here. AL has sustained damage to the left inferior occipito-temporal cortex including the fusiform, lingual and posterior parahippocampal gyrus (Fig. 1A). Laterally, the lesion extended into the inferior and middle occipital gyrus, and thus also affected the lateral occipital cortex (Fig. 1B and C). The patient had severe impairments of object recognition whether tested through the verbal (naming, object matching) or nonverbal (gesturing the object use) modality, but was able to identify objects by touch or when given a verbal description. He produced accurate copies, identified local differences between two similar objects independently of their orientation, matched shapes presented in canonical or noncanonical orientation and made correct decisions regarding 3D object structure from 2D-projections. AL had a comparable proportion of recognition errors for correctly and incorrectly colored objects – showing intact knowledge of color information, but his recognition was strongly affected by modulations of viewpoint or distortions of shape. He also failed when making categorical decisions about objects or when judging semantic relations between objects. In these tasks AL determined category membership based on global visual similarity, rather than on semantic knowledge. Thus, the patient had visual object agnosia characterized by intact elementary processing of local and global object shape, 3D structure and viewpoint-independent representations, but impaired access to object semantics necessary for categorization and identification.

2.2. Behavioral study

AL’s object identification errors were examined in seven

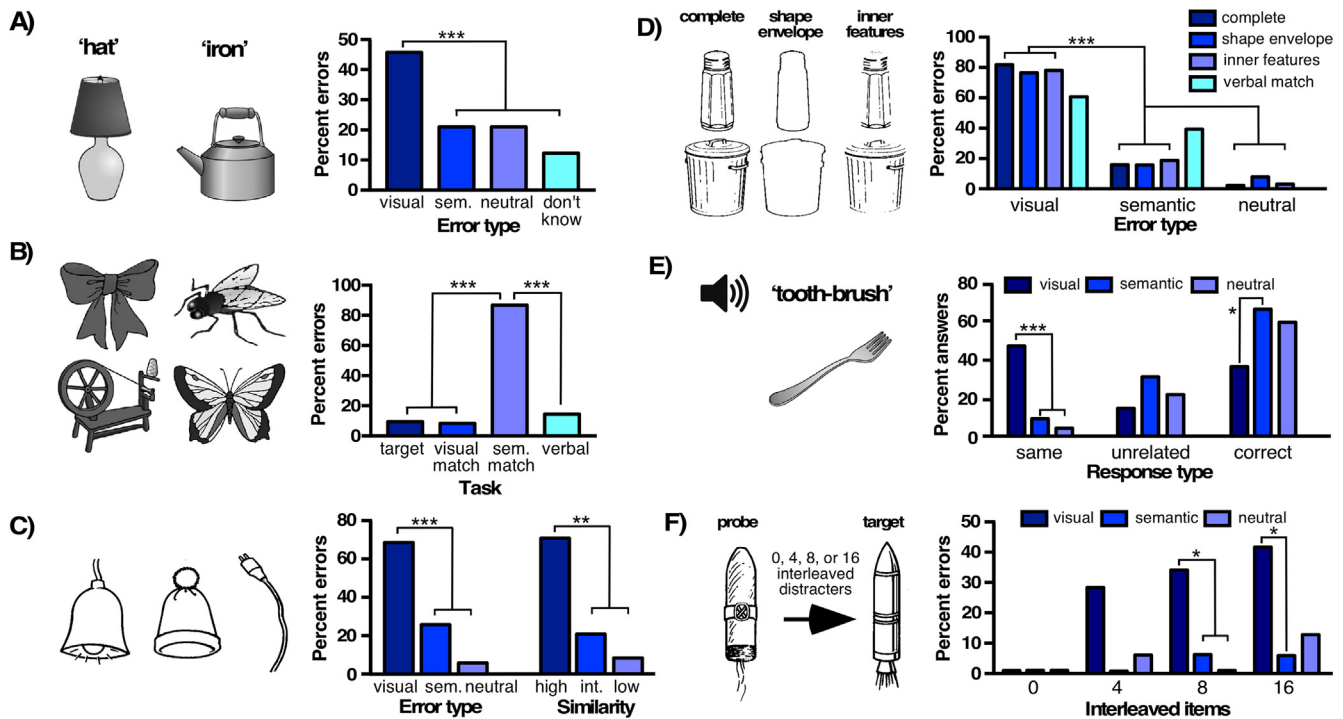


Fig. 2. Results of behavioral experiments. (A) Examples of naming errors produced by AL and percent errors in naming as a function of error type (Experiment 1; sem.: semantic). (B) A trial and results of the categorization experiment (Experiment 2). When asked to point to the two items belonging to the same semantic category (butterfly and fly) the patient would typically select the two similar items (butterfly and bow tie). He made significantly more errors when matching items semantically than when pointing to the target, when matching items visually, or when making a semantic match to verbally given items. (C) Example items of Experiment 3 (the two items on the left were used interchangeably as visually similar distracters). Percent errors were highest for visual distracters, and higher for distracters with high than intermediate or low visual similarity to the target. (D) Examples of items used in and results of Experiment 4. The patient confused the upper and lower item whether they were given in their complete form, only as shape envelopes or only with their inner features. (E) Example trial of Experiment 5. AL used the verbal label he had just heard more often when the label indicated a visually similar object to the target ('same' responses). In this condition he also made less correct responses. (F) Example trial and results of the object memory experiment (Experiment 6). AL showed increasing proportions of visual errors with increasing numbers of interleaved distracters.

experiments. Note that the data of experiments 1, 2 and 4 have partly been presented in a previous report (Ptak et al., 2014). The focus of the present study is on AL's identification errors because they inform us about the level of information he was still able to extract from visual representations.

2.2.1. Experiment 1: Picture naming

2.2.1.1. Material and procedure. Experiment 1 examined AL's naming of 260 line drawings (Snodgrass & Vanderwart, 1980), each shown on a sheet of paper in randomized order until a response was given (Fig. 2A). The patient was not given the correct answer as he showed a tendency to generate hypotheses about visual stimuli from verbal feedback, sometimes resulting in perseverations on previous responses.

2.2.1.2. Results. AL named only 46% (N = 122) of all pictures correctly. Errors were classified as visual, semantic, neutral (i.e., neither a visual nor a semantic connection with the target) and 'don't know'. Out of all errors those with a visual component were more frequent than all other error types ($X^2 > 17.76$, $p < .0001$), and semantic/neutral errors were marginally more frequent than 'don't know' responses ($X^2 = 3.16$, $p = .076$). Note that error classifications are often arbitrary as many responses may share at least a distant semantic connection even if errors are classified as visual (see examples of errors given in Fig. 2A). Based on AL's responses we therefore cannot isolate the semantic contribution to visual errors in naming.

2.2.2. Experiment 2: Categorization

2.2.2.1. Material and procedure. In Experiment 2 a target picture (e.g., an orange) of the Snodgrass picture set was shown together with a

visual (e.g., a ball), a semantic (e.g., grapes) and a neutral (e.g., a harp) distracter (see Fig. 2B for another example). The four items were arranged in a square and their position was determined randomly. There were 40 trials, and pictures were shown on a PC screen until AL responded. On three different occasions the patient was asked to (a) point to the target (orange), (b) point to the two items that shared the same shape (orange and ball), (c) point to the two items that belonged to the same category (orange and grapes). On a fourth occasion he was given the categorization task verbally: instead of showing him the four pictures, we provided the verbal labels of each of the four items and asked him to repeat those two belonging to the same category.

2.2.2.2. Results. AL made few errors when pointing to the target (12.5%) or the two visually similar items (7.5%), and when selecting two out of four verbally presented items belonging to the same category (17.5%). In contrast, he made 87.5% errors when given the semantic categorization task, most of which (80%) were visual errors (i.e., he pointed to the two visually similar instead of the two semantically related items). His error rate in the semantic categorization task was significantly higher than in all other tasks (Fisher test, all $p < .0001$). It is important to note that AL perfectly understood the concept of 'semantic relatedness', as he was able to make categorization judgments for items presented through the auditory modality.

2.2.3. Experiment 3: Verbal-visual matching

2.2.3.1. Material and procedure. Experiment 3 examined AL's capacity to discriminate a mental representation of an object with visually similar objects or items belonging to the same semantic category. We used a picture set drawn by a professional artist and developed for

testing of visuo-spatial capacities in aphasic patients (Gutbrod, 1987) that consisted of several highly similar objects/animals (Fig. 2C, F). On each trial three pictures were shown and the patient was asked to point to a verbally provided item (e.g., a belt) if he thought that it was present. In 80 trials the target was present and was always presented together with a neutral distracter (e.g., a telephone) and either a visual (e.g., a serpent) or a semantic (e.g., trousers) distracter. In 120 trials the target was absent and the display always contained a visual, a semantic and a neutral distracter. AL was explicitly informed that the target could be present or absent.

2.2.3.2. Results. On target-present trials AL made 16 (20%) errors, and in most of these trials (13) he indicated that the target was not present. When the target was absent AL incorrectly selected one of the three distracters in 35 (29%) trials. As shown in Fig. 2C his errors were mostly of the visual type, and were significantly more frequent than semantic or neutral errors ($\chi^2 > 11.89$, $p < .001$). Further, visual errors reflected the degree of similarity between the visual distracter and the target and were more frequent when visual similarity was high than when it was intermediate or low (Fisher test, $p < .01$).

2.2.4. Experiment 4: Verbal-visual matching without inner/outer features

2.2.4.1. Material and procedure. This experiment was similar to Experiment 3, but the pictures from the categorization experiment (Fig. 2B) were used. On each trial three pictures were presented, one of which was either the verbally designated target (target-present trials, $N = 80$) or a visual distracter (target-absent trials, $N = 160$). On target-present trials one distracter was always neutral, while the other distracter was visual or semantic. Target-absent trials always contained one visual, one semantic and one neutral distracter. In order to examine the influence of inner features and the outer shape on visual confusions, stimuli were either shown in their original (complete) form, with inner features removed (preserving only the shape envelope), or with the shape envelope removed (preserving only inner features). AL was asked to point to a verbally designated target (e.g. the garbage can), if he thought it was present. As in Experiment 3 he was explicitly told that the target might not be present among the three pictures. Finally, a fourth condition was run in which only one image was shown and AL was given three words, one of which could match the target, while the other two matched a visual, a semantic or a neutral distracter. For this control condition only the complete form of pictures was used. Note that in this condition the patient was also required to find a visuo-verbal match, but that choices were given in the verbal rather than the visual domain.

2.2.4.2. Results. On target-present trials AL pointed correctly to the target in 67 (83.8%) trials in the complete form, in 46 (57.5%) trials when only the shape envelope was shown and in 51 (63.8%) of all trials when only inner features were shown. When asked to choose a verbal match to a single target picture AL made the correct choice in 59 (73.8%) target-present trials.

In the critical target-absent condition AL made respectively 55% (complete form), 63.8% (shape envelope), 40% (inner features) and 35% (verbal match) errors. Note that this high proportion of false positive responses was produced despite explicit instructions that the target might not be present, which should induce conservative responding. Fig. 2D shows that errors were more frequent for visual compared to semantic and neutral distracters for complete pictures ($\chi^2 > 35.66$, $p < .0001$), shape envelope only ($\chi^2 > 35.51$, $p < .0001$), inner features ($\chi^2 > 20.27$, $p < .0001$), but not verbal matching ($\chi^2 < 1.8$).

2.2.5. Experiment 5: Verbal-visual priming

2.2.5.1. Material and procedure. This experiment examined further AL's capacity to identify correctly whether the naming of a visual target was influenced by the presentation of a verbal label shortly before. On each

trial ($N = 160$) the experimenter provided a verbal probe followed by a picture. AL's task was to name the picture irrespective of the probe, and he was informed that the probe did not necessarily match the target. The probe matched the target in 25% of all trials (match trials), while in the other 75% (non-match trials) it indicated either a visually similar, a semantically related, or a neutral object.

2.2.5.2. Results. When probe and target matched AL correctly named the target in 97.5% of all trials. Fig. 2D shows that instances in which AL correctly named the target despite being given a wrong verbal label were more frequent for semantically related ($\chi^2 = 5.01$, $p < .05$) and marginally more frequent for neutral ($\chi^2 = 3.2$, $p = .074$), compared to visually related probes. Conversely, he accepted visually related probes more often than semantic and neutral probes as indicators of the correct name for the target ('same' responses; both Fisher test, $p < .001$).

2.2.6. Experiment 6: Visual object memory

2.2.6.1. Material and procedure. This experiment evaluated the decay rate of visual representations of objects in AL. 14 items of the picture set used in Experiment 3 served as targets. For each target a probe item was selected that was either visually related, semantically related or neutral. In addition, a list containing 112 distracter images was created that were neither used as probes nor as targets. On each trial a probe was presented for 2000 ms, followed by 0, 4, 8 or 16 distracter images (each shown for 500 ms and followed by 200 ms blank period). The patient was then shown the target and was asked to indicate whether it depicted the same item as the probe. Thus, there were 16 conditions created by the orthogonal arrangement of the factors probe type (identical, visual, semantic, neutral) and number of distracters (0, 4, 8, 16), for a total of 336 trials.

2.2.6.2. Results. When the probe was identical to the target, the patient made respectively 95% (0 distracters), 100% (4 distracters), 83% (8 distracters) and 83% (16 distracters) correct responses. For targets that were distinct from the probe he made no error when there were no interleaved distracters between both images (Fig. 2F). When the probe was neutral or semantically related to the target, his error rate remained constant in conditions with 4, 8 and 16 distracters. In contrast, for visually similar probes the patient made a steadily increasing number of errors with increasing numbers of distracters. With 4 distracters visual errors tended to be more frequent than semantic errors (Fisher's test, $p = .097$), while with 8 distracters they were significantly more frequent than semantic and neutral errors (Fisher's test, $p < .05$) and with 16 distracters more frequent than semantic errors (Fisher's test, $p < .05$).

2.2.7. Experiment 7: Lexical decision

2.2.7.1. Material and procedure. All previous experiments have shown that AL had a strong tendency to confound visually similar items, as compared to semantically related or neutral items. The final experiment examined whether his representations of object shape would facilitate access to lexical representations. We tested the effects of the presentation of an object on lexical decision. From the picture set used in Experiment 3 we selected 15 objects as targets and the same number of visually similar, semantically related and neutral images. All 60 images would be used as primes, while the names of the target images served as lexical decision targets. For each name a nonword was created by rearranging randomly the letters of the target word (e.g. 'graci' for cigar). In order to exclude effects of linguistic variables pictures were selected so that the frequency and length of their corresponding names be comparable between the four prime conditions. One-way ANOVAs confirmed that neither frequency ($F(3, 57) = 0.48$) nor word length ($F(3, 57) = 0.09$) differed between the four conditions.

On each trial a prime was shown for 50 or 1000 ms, followed by a blank period (500 ms) and the target word/nonword until the patient

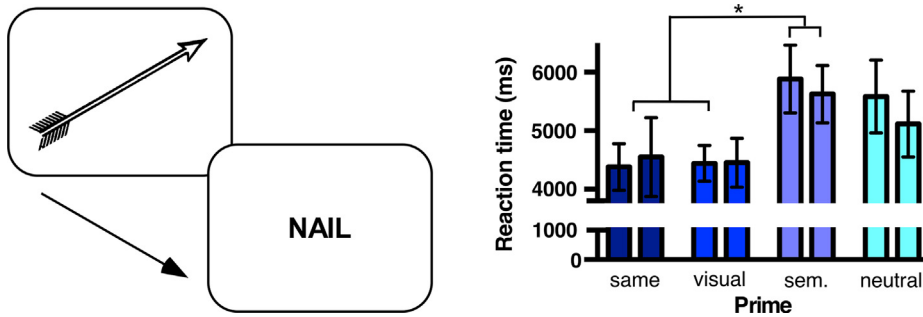


Fig. 3. Lexical decision task (Experiment 7). In the example shown on the left AL was asked to press as quickly as possible a button when he thought that the letter sequence formed an existing word (image not shown to scale). Reaction times were faster when the prime was the same or a visually similar item as the target word than when it was semantically related. The left and right bars for each type of prime show RTs for short (50 ms) and long (1000 ms) prime durations, respectively.

responded. For example, for the upcoming French word 'loupe' (magnifying glass) a picture of a magnifying glass was shown in the same condition, the picture of a mirror in the visual condition, the picture of glasses in the semantic condition and the picture of a tent in the neutral condition. AL was asked to press as quickly as possible the space bar when he thought that the letter string on the screen represented a word.

2.2.7.2. Results. Fig. 3 shows that in accordance with his alexia AL's reaction times in the lexical decision task were exceedingly slow, varying between 4 and 6 s (which is at least ten times slower than what would be expected for normal readers). A two-way ANOVA with the factors prime duration (50 ms, 1000 ms) and prime type (same, visual, semantic, neutral) revealed no effect of prime duration ($F_{1,296} = 0.19$), but a significant effect of prime type ($F_{3,296} = 3.03$, $p < .05$). Post-hoc least significant difference tests showed that RTs were significantly faster following same ($p < .05$) and visual ($p < .05$) compared to semantic primes. In addition, AL had a tendency for faster reactions following same compared to neutral, ($p = .088$), and visual compared to neutral primes ($p = .081$).

2.3. Functional connectivity study

2.3.1. Material and procedure

The present study reanalyzed fMRI data that had been acquired with AL and four age-matched control subjects in the context of a brain-activation study. The use of active-state data to 'emulate' resting-state fMRI is feasible provided one removes variance in the BOLD time series that is directly related to the task conditions (Fair et al., 2007). These analyses rest on the assumption that task-evoked activity is linearly added to a continuous underlying 'resting' signal. By entering the main effects of task conditions as confounds during data preprocessing one should therefore be able to separate task-evoked activity from spontaneous BOLD fluctuations. It is important to note that if task-related variability differs between the patient and controls its removal may have different effects on the remaining signal. For example, task-evoked signals may affect functional connectivity more in the patient than in controls; removing it may therefore partial out more of relevant variance in the former than the latter. On the other hand, task-induced correlations may contaminate the supposed underlying 'resting' correlations, and this contamination would differ between the patient and controls if task-related variance differed. For example, if the patient was relatively more affected than controls by the task conditions, keeping task-induced activity for the connectivity analyses might lead to exaggerated estimates of connectivity in the patient. We here preferred a conservative approach and therefore found it safer to stick to the method proposed by Fair et al. (2007) by partialling out the task-induced effects.

The data were obtained during a single scanning session and consisted of three data blocks, in which alternating epochs of varying stimuli were presented in four conditions: (1) grey-scale photographs of everyday artifacts and tools, (2) faces, (3) houses and other buildings, and (4) scrambled images. Each epoch lasted 24 s, during which nine images were shown. Some epochs contained nine different images,

while in other epochs three images were repeated three times or the same image was repeated nine times. The overall duration of scanning used for analysis was 19.6 min. T2*-weighted GRE echo planar imaging sequences and a high-resolution MPRAGE T1-weighted sequence were acquired on a 3 T Trio scanner (Siemens Medical Solutions, Erlangen, Germany). Preprocessing was performed in SPM 12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>) and involved head-motion correction, coregistration to the anatomical reference scan, segmentation and normalization to MNI-reference space, smoothing (4 mm FWHM Gaussian kernel) and high-pass filtering to remove physiological artifacts and drift. In order to preserve slow BOLD fluctuations no low-pass filter was applied to the data. Seed-based FC analyses were performed using the CONN-toolbox (<https://www.nitrc.org/projects/conn>; Whitfield-Gabrieli & Nieto-Castanon, 2012). Based on the AAL atlas (Tzourio-Mazoyer et al., 2002) we defined several regions of interest (ROI) as seed-ROIs in the right (preserved) hemisphere centered on the lateral occipital and inferior occipito-temporal cortex: the fusiform and lingual gyri and the inferior occipital and middle occipital region (see Fig. 1). These ROIs were of particular interest since they were homologous to the injured left occipito-temporal cortex and cover object-selective LOC. In addition, we also examined intrahemispheric and interhemispheric connectivity of other right-hemisphere regions: calcarine sulcus, precuneus and cuneus, as well as superior occipital cortex.

For all analyses we computed Fisher-transformed correlation coefficients between seed-ROIs and each other voxel of the brain. For this analysis a linear regression model was created by introducing the 6 rigid-body parameters estimated from realignment, white-matter BOLD signal, cerebro-spinal fluid masks and experimental conditions as covariates to remove noise from physiological sources, task-related coactivation and other artifacts. The significance of standardized correlation coefficients was examined in a within-subject (patient) and within-group (controls) design using paired t-tests. Results were thresholded at voxel-level using $p < .001$ (uncorrected) and at cluster-level with family-wise error corrected $p < .05$.

2.3.2. Results

Fig. 4 shows cross-correlation matrices of connectivity between right-hemisphere seed ROIs and ipsilateral or contralateral destination areas. We compared AL's correlation coefficients to controls with t-tests as proposed by Crawford and Howell (1998) when comparing an individual score against a small sample. AL showed a strong decrease of contralateral connectivity between right inferior and middle occipital and left inferior occipital, fusiform and lingual cortex. Additionally, decreased connectivity was measured between right cuneus and left calcarine sulcus and lingual gyrus. However, there was also increased connectivity between AL's right occipital cortex and his left cuneus and precuneus. Decreased connectivity was observed between inferior occipital and ipsilateral right fusiform cortex, whereas the right cuneus and precuneus showed compensatory increases of connectivity with ipsilateral inferior and superior occipital cortex.

Fig. 5 shows a detailed analysis of connectivity of right-hemisphere lingual, fusiform, inferior and middle occipital cortex with the rest of

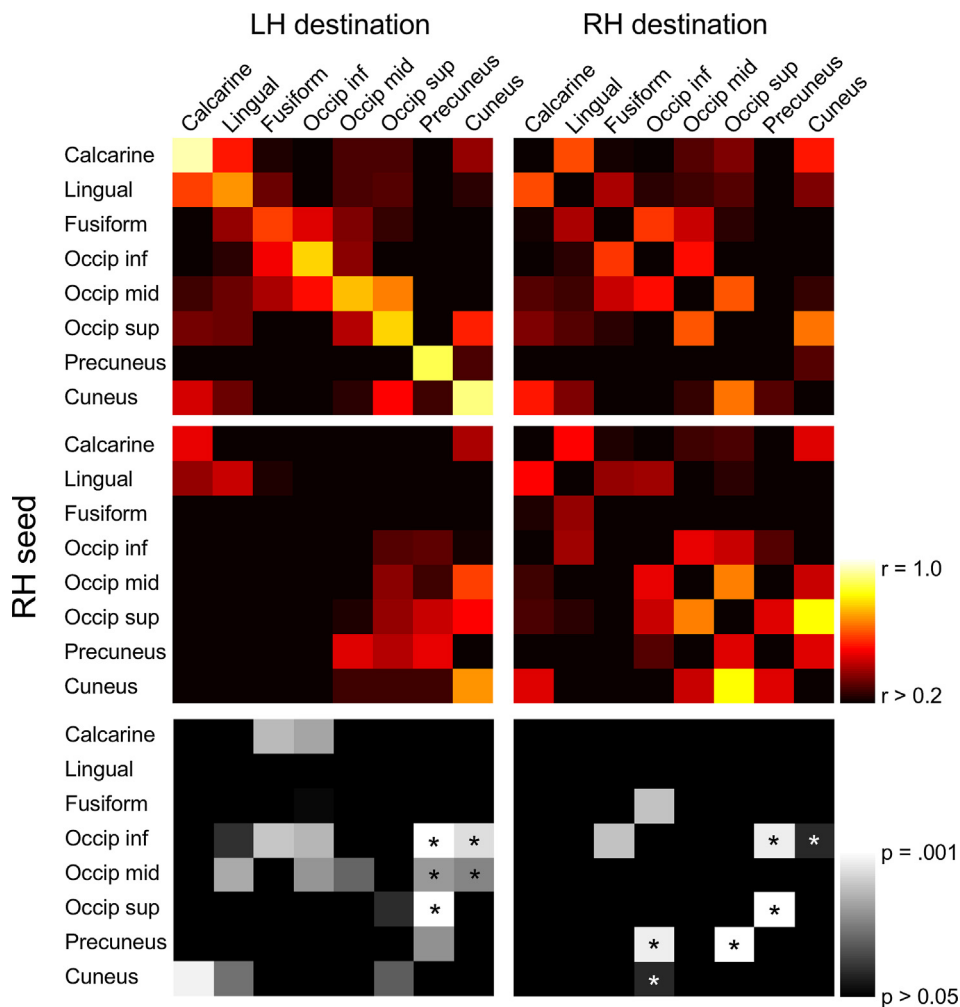


Fig. 4. Cross-correlation matrix representing color-coded standardized correlation coefficients between seed-ROIs of the right hemisphere and destination areas lying in the left or right hemisphere (upper row: healthy controls; middle row: AL). The bottom row shows results of t-tests comparing connectivity of the patient against the control groups. Squares marked with an asterisk indicate areas where connectivity in AL was increased relative to controls, while unmarked squares show areas of decreased connectivity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the brain. Control participants showed significant connectivity between all ROIs and left homologous visual cortex as well as left inferior and anterior temporal cortex. In contrast, AL exhibited some connectivity of the right lingual and fusiform gyrus with homologous cortex in the left hemisphere, but no significant connectivity with more anterior temporal cortex. The most striking finding was the absence of connectivity between right inferior and middle occipital cortex (corresponding to the LOC) and left occipito-temporal cortex.

3. Discussion

The present findings provide evidence that may reconcile observations of patients showing object processing deficits following focal damage to visual cortex with the view that visual object knowledge depends on neural mechanisms distributed across both cerebral hemispheres. Previous studies have shown that visual object agnosia may mainly be associated with bilateral or unilateral left damage. According to an early literature review 65% of 48 cases with an object recognition deficit had bilateral damage against 27% cases with unilateral left and only 8% with unilateral right damage (Farah, 1991). Detailed structural imaging studies revealed in several patients damage to the left parahippocampal, lingual and fusiform gyrus (Feinberg, Schindler, Ochoa, Kwan, & Farah, 1994), though one particularly well-studied patient had isolated damage to the right posterior fusiform

gyrus (Konen et al., 2011). How this complex pattern of brain damage may fit with the idea of distributed coding of visual object knowledge has so far eluded an explanation. Based on the present investigation, we propose that visual object agnosia in our patient was consecutive to a breakdown of interhemispheric FC following unilateral left damage.

Our patient showed characteristic object recognition deficits whether he was tested with real objects or line drawings (Ptak et al., 2014). When considering the broad distinction between apperceptive (i.e., affecting elementary visual processing; Cavina-Pratesi, Kentridge, Heywood, & Milner, 2010; Goodale, Milner, Jakobson, & Carey, 1991) and associative visual agnosia (i.e., affecting later stages of processing, in particular the access to semantics of object shape; Farah, 2004) AL's object agnosia conforms to the associative type. However, as shown by several previous case studies this coarse nosological categorization does not exclude subtle deficits in processing visual shape characteristics (Anaki et al., 2007; Behrmann & Kimchi, 2003; Delvenne, Seron, Coyette, & Rossion, 2004). In agreement with these findings our patient also showed slight, but significant impairments in the processing of shape information despite being able of copying global and local shape features adequately. The present behavioral experiments focused on his errors, which inform us about his processing biases and adaptive strategies that may lead to specific object recognition failures. AL produced primarily visual errors in picture naming (Experiment 1), and he classified pictures of objects according to their visual similarity, rather than

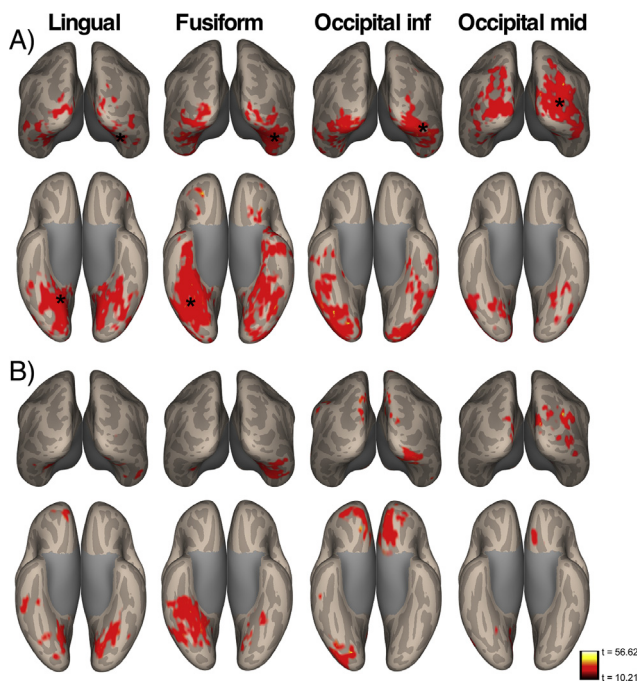


Fig. 5. Functional connectivity of four right-hemispheric seed regions with every other voxel of the brain in (A) healthy controls and (B) patient AL (asterisks show approximate location of the seed-ROI).

semantic category (Experiment 2). This finding suggests that the patient did not have access to semantic representations through the visual modality, and therefore had to rely on visual information for any decision concerning the category of objects. In addition, when a target was not present AL frequently pointed to a visual distracter, though he had the choice to give no response (Experiments 3 and 4). Thus, AL's decisions concerning object identity were guided by general knowledge of the shape envelope (such as whether an object was round or elongated) rather than associated semantic information. This was confirmed in Experiment 5, which showed that AL accepted a verbal label for an object when the label defined a visually similar, rather than a semantically related or neutral object. Experiment 6 further showed that visual distracters led to an increase of visual errors when the patient was required to compare two sequentially presented objects, indicating that AL's confusion of objects is favored by visual interference. Finally, Experiment 7 showed that AL's tendency to favor shape information of objects in expense of their semantic features affected his responses even when implicit processing of object associations was required in a lexical decision task. Together, these experimental findings indicate that AL's object agnosia reflects the inability to access semantic representations through the visual modality and the tendency to make categorical decisions and object comparisons based on automatic activation of object shape.

When discussing the anatomical bases of visual agnosia early studies considered the possibility that the deficit may be the result of structural disconnection. According to one hypothesis, a combination of damage to left occipito-temporal cortex (leading to right homonymous hemianopia) and the callosal splenium would isolate the right hemisphere and thus prevent access to left-hemispheric categorical and descriptive semantic knowledge (Benson, Segarra, & Albert, 1974; Geschwind, 1965). Another proposal is that visual representations elaborated in the occipital cortex become disconnected from semantic knowledge located in the temporal lobes (Anaki et al., 2007). However, in light of the observation that left, bilateral or even unilateral right damage may lead to agnosia, such explanations were difficult to maintain (Albert, Soffer, Silverberg, & Reches, 1979).

Our functional connectivity results reveal that even in the absence

of evidence for a structural disconnection, object-processing deficits reflect changes of functional connectivity of right and left occipito-temporal cortex. The most striking feature of AL was significantly decreased FC between the left hemisphere seed and right visual cortex as well as decreased FC between the right occipital seed and the left occipito-temporal cortex. In addition, he exhibited similar differences in FC of the right occipito-temporal seed region with frontal cortex, reflecting impaired interhemispheric, intrahemispheric and posterior-anterior connectivity. Interestingly, AL also showed *increased* connectivity relative to controls between dorsal occipital cortex and the medial parietal cortex, possibly suggesting local compensatory adaptations.

In a previous study of AL we found that his intact right lateral occipital cortex was activated when he was viewing faces, while this region showed no significant activation when he was shown objects (Ptak et al., 2014). This breakdown of activity is reminiscent of the lack of contralesional activation in a patient with object agnosia following right fusiform damage (Konen et al., 2011) and similar deactivations of occipito-temporal cortex observed in a developmental agnosic patient (Gilaie-Dotan, Perry, Bonne, Malach, & Bentin, 2009). In the latter patient the authors also observed that the deactivated visual cortex was less well connected with the rest of the brain (Gilaie-Dotan et al., 2013), suggesting that cortico-functional adaptations of brain activity co-occur with changes in FC. Thus, the decrease of activity to specific classes of visual stimuli is a neural marker of visual processing deficits in object agnosia and is associated with modifications of FC in regions central for the processing of object shape. The fact that our patient had focal left-hemispheric damage suggests the more specific conclusion that the absence of right-hemispheric activation to objects was due to the distant damage of homologous regions of the left hemisphere – a form of functional disconnection.

The findings of our study thus provide a solution of the apparent controversy outlined in the introduction, between the view that visual cortex is organized based on specialized modules for domain-specific knowledge (Downing et al., 2006; Kanwisher, 2004) and the proposal that neural coding of visual information is distributed across regions covering both cerebral hemispheres (Haxby et al., 2001; Ishai et al., 1999). At the behavioral level our patient had access to adequate and detailed representations of object shape while being unable to provide semantic knowledge, which is reminiscent of the characterization of object agnosia as a 'percept stripped of its meaning' (Teuber, 1968). Previous studies have shown that activations of lateral occipital cortex differ for visually similar and dissimilar shapes at the local (i.e., features) and global level (shape envelope) (Drucker & Aguirre, 2009; Op de Beeck, Torfs, & Wagemans, 2008). The present findings suggest that this capacity depends on the coupling of activity and cooperation between the left and right hemisphere. Our examination of AL's identification errors suggests that his visual analysis remains focused on global shape features such as outline curves, lines or edges, which are not sufficiently distinctive to activate precise concepts. The FC analyses provide further evidence for this interpretation, as AL not only showed FC decreases between left and right visual cortices, but also changes of connectivity between occipital, temporal and prefrontal cortex. This finding suggests that visual computations remained relatively isolated to posterior cortex and therefore failed to connect to regions representing associative object knowledge.

In sum, the present findings link up with the recent proposal that representations of object shape depend on distributed coding of information across bilateral occipito-temporal cortex (Behrmann & Plaut, 2013). According to this view shape selectivity reflects the concurrent activation of distributed visual areas, some of which are optimized for a specific class of visual stimuli, while others are more loosely associated with processing of these stimuli. The resulting functional specialization is thus an emergent property of the activation of the whole system, which may break down when an optimized part of the system is damaged – as shown in the present case of object agnosia.

Acknowledgement

Study supported by the Center for Biomedical Imaging (CIBM) of the Universities of Geneva and Lausanne, the EPFL and the University Hospitals of Geneva and Lausanne and grants from the Swiss National Science Foundation (grant 320030-152689) and the Novartis Foundation (grant 16C183) to RP.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bandc.2018.12.007>.

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