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Visual and cross-modal cues increase the identification of overlapping visual stimuli in Balint's syndrome

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ABSTRACT

Introduction: Cross-modal interactions improve the processing of external stimuli, particularly when an isolated sensory modality is impaired. When information from different modalities is integrated, object recognition is facilitated probably as a result of bottom-up and top-down processes. The aim of this study was to investigate the potential effects of cross-modal stimulation in a case of simultanagnosia. *Method*: We report a detailed analysis of clinical symptoms and an ^{18}F-fluorodeoxyglucose (FDG) brain positron emission tomography/computed tomography (PET/CT) study of a patient affected by Balint's syndrome, a rare and invasive visual–spatial disorder following bilateral parieto-occipital lesions. An experiment was conducted to investigate the effects of visual and nonvisual cues on performance in tasks involving the recognition of overlapping pictures. Four modalities of sensory cues were used: visual, tactile, olfactory, and auditory. *Results*: Data from neuropsychological tests showed the presence of ocular apraxia, optic ataxia, and simultanagnosia. The results of the experiment indicate a positive effect of the cues on the recognition of overlapping pictures, not only in the identification of the congruent valid-cued stimulus (target) but also in the identification of the other, noncued stimuli. All the sensory modalities analyzed (except the auditory stimulus) were efficacious in terms of increasing visual recognition. *Conclusions*: Cross-modal integration improved the patient's ability to recognize overlapping figures. However, while in the visual unimodal modality both bottom-up (priming, familiarity effect, disengagement of attention) and top-down processes (mental representation and short-term memory, the endogenous orientation of attention) are involved, in the cross-modal integration it is semantic representations that mainly activate visual recognition processes. These results are potentially useful for the design of rehabilitation training for attentional and visual–perceptual deficits.

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Experimental evidence indicates that objects characterized by redundant multisensory cues are identified more rapidly than the same objects presented in a unimodal condition (Amedi, von Kriegstein, van Atteveldt, Beauchamp, & Naumer, 2005). This suggests that object identification in one modality is influenced by input from other modalities.

To date, this cross-modal integration effect has mainly been investigated in visuoacoustic modalities (Chen & Spence, 2011; Fort, Delpuech, Pernier, & Giard, 2002; Pascucci, Megna, Panichi, & Baldassi, 2011; Schneider, Engel, & Debener, 2008). However, cross-modal facilitation has also been demonstrated for synchronous auditory–tactile (Gillmeister & Eimer, 2007), visuotactile (Helbig & Ernst, 2007), and visuo-olfactory (Gottfried & Dolan, 2003) stimulation.

Cross-modal interactions are modulated by both the nature of the perceptual task and the sensory skills of individuals (Fort et al., 2002). This type of interaction is particularly efficient in terms of improving perceptual performance when an isolated modality is deficient (Caclin et al., 2011). For this reason, the study of cross-modal facilitation in patients affected by perceptual and attentional diseases may offer important information for clinical

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assessment, rehabilitation, and compensatory strategies.

Balint's syndrome (BS) is a specific disorder affecting visuospatial attention (Hécaen & De Ajuriaguerra, 1954). It is usually the result of lesions in the bilateral parieto-occipital areas, but has also been reported after damage involving frontal areas (Hausser, Robert, & Giard, 1980) and pulvinar (Ogren, Mateer, & Wyler, 1984). BS was initially described in a patient suffering from "progressive cerebrovascular complications" (Bálint, 1909; Rizzo & Vecera, 2002) and later reported after traumatic brain injury, posterior cortical atrophy, tumors, prion disorders (e.g., Creutzfeldt–Jakob disease), and viral infections such as HIV (for a review, see Rizzo & Vecera, 2002).

Three deficits (not always associated) represent core symptoms: ocular apraxia, optic ataxia, and simultanagnosia (Rizzo & Vecera, 2002).

The term ocular apraxia indicates a lack of organization in voluntary eye movements, with prolonged static fixations and dysfunctional gaze shifting (Rossetti, Pisella, & Vighetto, 2003). When optic ataxia occurs, oculomotor coordination is impaired, in the absence of motor, sensory, or visual acuity or visual field disorders (Karnath & Perenin, 2005). This makes it very difficult or impossible to execute visually goal-directed movements of the hands, such as reaching and grasping objects in the peripersonal space. Finally, simultanagnosia (Wolpert, 1924) refers to an inability to explore complex visual images and to perceive multiple objects and the relationship between them. The processing of individual items and local features is, however, spared.

Literature on BS mainly refers to single-case reports. This is due both to the low frequency of the syndrome and to the fact that typically there are bilateral large lesions, usually responsible for extensive sensory and cognitive symptoms, all of which hinder specific assessments.

We had the opportunity to carry out extensive research on M.R., a young man affected by BS (stable over time) as a consequence of anoxic cerebral damage. He was keen to participate in our study. In addition to an in-depth neuropsychological assessment and an ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) study, we devised an experimental procedure in order to investigate the potential effects of cross-modal integration on his performance in the identification and denomination of two objects shown in overlapping images.

Previous studies have investigated the role of visuotactile facilitation in spatial representation (Valenza, Murray, Ptak, & Vuilleumier, 2004). Nevertheless, to the best of our knowledge, the effects of cross-modal processing in simultanagnosia have never before been investigated. Starting from the data indicating that the perception of external stimuli is supported by cross-modal integration, in particular when isolated sensory modalities are impaired (Pascual-Leone, Amedi, Fregni, & Merabet, 2005), we hypothesized that cross-modal stimulation would enhance M.R.'s ability to detect and recognize overlapping visual images.

In order to test the hypothesis that various different sensory stimuli would induce benefits for our patient, we devised an ad hoc experimental paradigm. A single stimulus (cue) was first presented in one of four sensory modalities (visual, tactile, olfactory, and auditory). This cue was then followed by a visual image showing two overlapping objects. In some trials the cue represented one of the two objects shown in the overlapping figures (valid cue, congruent trial), while in other trials it was a totally different object (invalid cue, incongruent trials).The patient was asked to identify both of the objects in the overlapping images. The effects of the cues were measured by means of a comparison between M.R.'s responses in valid and invalid trials.

Since the cue was always one single stimulus (visual, tactile, olfactory, or auditory), we anticipated that it would not be difficult to identify. We also predicted that in congruent valid trials, if the patient recognized the initial cue (regardless of the sensory channel), it would help him to identify the target (previously cued) object in the overlapping figures. It should also make it easier for the patient to segregate and recognize both of the two objects in the overlapping figures. For this reason, it was further anticipated that he might also be able to identify the second, noncued object in the valid congruent trials.

Lastly, due to the similarity between the cues and the corresponding objects in the overlapping figures in the visual modality, we foresaw a greater effect of the visual cues with respect to the cues administered in the other sensory modalities.

1. Method

1.1. Case report

M.R. is a 40-year-old, right-handed man who worked as a manual worker (8 years of education).

As a consequence of cardiac arrest (30–40 s), which occurred 5 days after a surgical operation, he suffered an anoxic brain injury. A CT scan (3 days from onset) revealed hypodensity in the cortical and subcortical bilateral parieto-occipital transition, in the right frontoparietal and left rolandic areas.

A month after the onset of the lesion, M.R. appeared to be not totally oriented in time and space and not fully aware of his condition. The left side of his body was weak but there were no paralysis or sensory deficits. There were massive disorders in ocular motricity and when he reached for objects using his hands, in addition to nontestable difficulties in exploring the left visual field and minimal deficits in object recognition. During conversation he showed anomies and phonemic paraphasias, with alexia and agraphia.

The procedure of the study was approved by the local ethics committee (Comitato Etico Provinciale, Verona), and informed written consent concerning the participation in the experiments was obtained from the patient.

1.2. General neuropsychological assessment

Two months after the stroke, a computerized campimetric examination indicated only a few small patches of reduced sensitivity in the visual field. Horizontal and vertical ocular movements were normal. General cognitive functions and temporal orientation appeared to have been spared, although a global slowness in verbal and motor responses was evident. Initial signs of spatial neglect and apraxia had recovered. M.R. complained of difficulties in object discrimination. As a result of this, a first assessment of visual agnosia was carried out (Table 1).

Four months after onset, at the time of the experimental procedure, M.R. underwent a further assessment for visual agnosia, neglect, language, memory, and executive functions (Tables 1 and 2). His deficits in visual recognition were confirmed, in particular in a subtest involving the recognition of multiple and overlapping images (Table 1) and in the examination involving the visual extinction of double stimuli. In addition, M.R. showed executive function deficits in tasks involving short-term memory, phonemic fluency (Frontal Assessment Battery, FAB, subtest of fluency score = 1), and task planning (Table 2).

Table 1. Neuropsychological assessment of visual agnosia.

Test	Items (*N*)	2 months	4 months	Cutoff
Agnosia Battery[a]				
Efron Test	20	20	18	16.51
Figure–ground discrimination	33	**16**	**24**	29.03
Overlapping images test (Ghent)	40	**4**	**24**	36.51
Incomplete images test: short (Gollin)	75	**imp**	**38**	58.56
Matching objects	40	**23**	*30*	30.79
Chimeric images	48	**32**	*41*	41.99
Color naming	40	**35**	*36*	36.16
Associative match task	20	**12**	19	17.92
Semantic test: short	240	236	235	234.09
Picture naming	40	**35**	*37*	37.67
Object denomination[b]	33	30	—	—
BORB[c]				
Length match	30		*24*	24
Size match	30		*23*	23
Orientation match	30		21	20
Position of gap	40		34	27
Letters (s)	36		36 (**1.58**)	(0.4)
Paired nonoverlapping (s)	36		35 (**1.42**)	(0.4)
Paired overlapping (s)	36		35 (**0.97**)	(0.4)
Triples nonoverlapping (s)	36		32 (**2.5**)	(0.4)
Triples overlapping (s)	36		28 (**3.47**)	(0.4)
Geometrical shape (s)	36		32 (**5.05**)	(1.0)
Paired nonoverlapping (s)	36		35 (**3.08**)	(1.1)
Paired overlapping (s)	36		33 (**2.75**)	(1.1)
Triples nonoverlapping (s)	36		30 (**4.05**)	(1.2)
Triples overlapping (s)	36		34 (**3.97**)	(1.3)

Note. N is the number of items for each test. Pathological scores are in bold; in italics are the scores at cutoff or where the time of execution is slower than normative data. BORB = Birmingham Object Recognition Battery; imp = impossible. The BORB's scores indicate the patient's accuracy. Values in parentheses indicate average execution time per item.

[a]Battery Test for Agnosia (Italian version; Barletta-Rodolfi, Ghidoni, & Gasparini, 2011) at 2 and 4 months; [b]Additional clinical test of denomination of real objects; [c]Birmingham Object Recognition Battery (Riddoch & Humphreys, 1993) at 4 months.

1.3. Balint's syndrome

Following the seminal case report by Balint (Bálint, 1909; reported in Vallar & Papagno, 2007), three main symptoms were investigated separately: ocular apraxia, simultanagnosia, and visuomotor processing.

1.3.1. Ocular apraxia

In the acute phase, ocular apraxia was manifested in M.R.'s inability to read, write, and visually follow lines. These disorders recovered during the first few months. At the time of our second evaluation (4 months from the onset), M.R. was able to follow specific directions with his eyes on verbal command, though with some minimal hesitation on the left side. Nevertheless, M.R. was not able to voluntarily gaze at the surrounding space. In

Table 2. General neuropsychological assessment.

Task	MR's scores	Cutoff/ES
Neglect		
Reading	+	
Writing	+	
Barrage	+	
Drawing Copy	+	
Clock Test[a]	13	7.57
Visual extinction	—	
Language		
Denomination of pictured compound nouns (AAT[b])	30	
Denomination of pictured sentences (AAT[b])	27	
Memory		
Short-term spatial memory (Corsi[c])	**2.5**	3.75
Long-term spatial memory (Corsi[c])	17.2	10.25
Short-term verbal memory (Word Span[c])	**2.5**	3
Story Recall[c]	11.1	4.75
Executive functions		
FAB[d]	16.85	12.03
BADS[e]	**11**	18.6
Rule shift cards (ES 0–4)	*3*	≥2
Action program (ES 0–4)	*3*	≥2
Key search (ES 0–4)	**2**	≥2
Temporal judgment (ES 0–4)	**1**	≥2
Zoo map (ES 0–4)	**0**	≥2
Modified six elements (ES 0–4)	**2**	≥2
Verbal judgment[c]	42.5	33
Tower of London[f]	**24**	26.54

Note. M.R.'s scores in batteries that assess neglect,[a] language,[b] memory,[c] and executive functions (Frontal Assessment Battery, FAB;[d] Behavioural Assessment of the Dysexecutive Syndrome, BADS, Italian Version;[e] Tower of London, ToL[f]) are reported. ES = equivalent score; + denotes normal performance; – denotes pathological performance. Pathological scores are in bold; scores at cutoff are in italics. AAT: Aachen Aphasia Test.
[a]Caffarra et al., 2011. [b]Luzzatti, Willmes, & De Bleser, 1996. [c]Spinnler & Tognoni, 1987. [d]Appollonio et al., 2005. [e]Shallice, 1982; Spitoni, Antonucci, Orsini, D'Olimpio, & Cantagallo, 2002. [f]Allamanno, Della Sala, Laiacona, Pasetti, & Spinnler, 1987.

addition, he failed to pursuit eye movements, and he could not move his eyes properly in order to identify small differences in the lengths of two or more objects (e.g., the task involving the discrimination between the lengths of two sticks, Table 3) or to single out one object among others (Table 3).

1.3.2. Simultanagnosia

The patient complained that he found it difficult to explore space and complex, multipart objects, in comparison to normal abilities to recognize and name simple, individual objects, real or represented in pictures. At the first assessment, M.R. failed in the task of visual extinction of double stimuli, where he always missed one of the two stimuli presented simultaneously. He was able to perceive only one of the stimuli at a time, either the one on the right or the one on the left but not both at once. At 2 months from lesion onset, he still failed in a task in which he was requested to identify and count objects placed closely together (i.e., identification of the number of objects, Table 3). Moreover, M.R. could not discriminate the reciprocal position of two real objects superimposed (e.g., identifying whether a spoon was in front of or behind a fork). He also failed to discriminate the two separate parts of a chimeric image. Finally, he was unable to describe a complex scene as a whole, stating that he saw some separate parts of the image but without being able to integrate them into one image. In effect, M.R. manifested two apparently opposite deficits: He was unable to integrate individual picture-parts but he was also unable to identify the individual elements of a complex image. For example, he did not realize that a complex image he was shown represented a coffee bar (with typical furniture and objects, a waiter, and a customer) and was also unable to detect the presence of two individual elements (e.g., a donkey and a key, see video in Supplementary Material).

Table 3. Clinical assessment of Balint's syndrome.

Task	Trials (*N*)	Correct responses (%)
Ocular apraxia		
Sorting the length of multiple objects (sticks)	10	**50**
Length discrimination of two sticks	19	**31.58**
Simultanagnosia		
Identification of the numerosity of objects	5	**0**
Discrimination of the reciprocal position of two objects	47	**57.48**
Visuomotor processing		
Optic ataxia RH	8	100
Optic ataxia LH	13	84.61
Pointing at objects RH	45	**73.33**
Pointing at objects LH	45	**48.89**
Pointing with a tool RH	15	**33.33**
Pointing with a tool LH	15	**26.67**
Pointing at overlapping objects RH	15	**66.67**
Pointing at overlapping objects LH	15	**73.33**
Grasping with RH	15	**80**
Grasping with LH	15	**60**

Note. The percentages of M.R.'s correct responses in tasks assessing optic apraxia, simultanagnosia, and visuomotor processing are reported. *N* is the number of trials for each task; RH = right hand; LH = left hand. Pathological scores are in bold.

1.3.3. Visuomotor processing

M.R. could grasp moving objects that were placed in his right or left hemifield (optic ataxia—Karnath & Perenin, 2005) without problems. In contrast, he failed to point at and grasp static objects (e.g., a pen or a fork) with either his right or his left hand, and his performance worsened when he pointed at objects using an instrument of some sort (e.g., a pencil).

1.4. Neuroimaging data from ^{18}F-FDG brain PET/CT

The examination was carried out by a highly experienced physician of nuclear medicine (Ma. S.) 2 months after the lesion onset (for technical details, see Figure 1). Areas of hypometabolism were found in bilateral parietal areas across both the parieto-occipital and the temporoparietal transitions (Figure 1). These areas have been previously described in patients suffering from BS (Phan, Schendel, Recanzone, & Robertson, 2000; Rizzo & Vecera, 2002). A specific investigation of the site of the lateral occipital complex (LOC), which is specialized in the recognition of individual objects (Malach et al., 1995), confirmed that this area was spared. In fact, M.R. did not show any disorders in his perception of individual

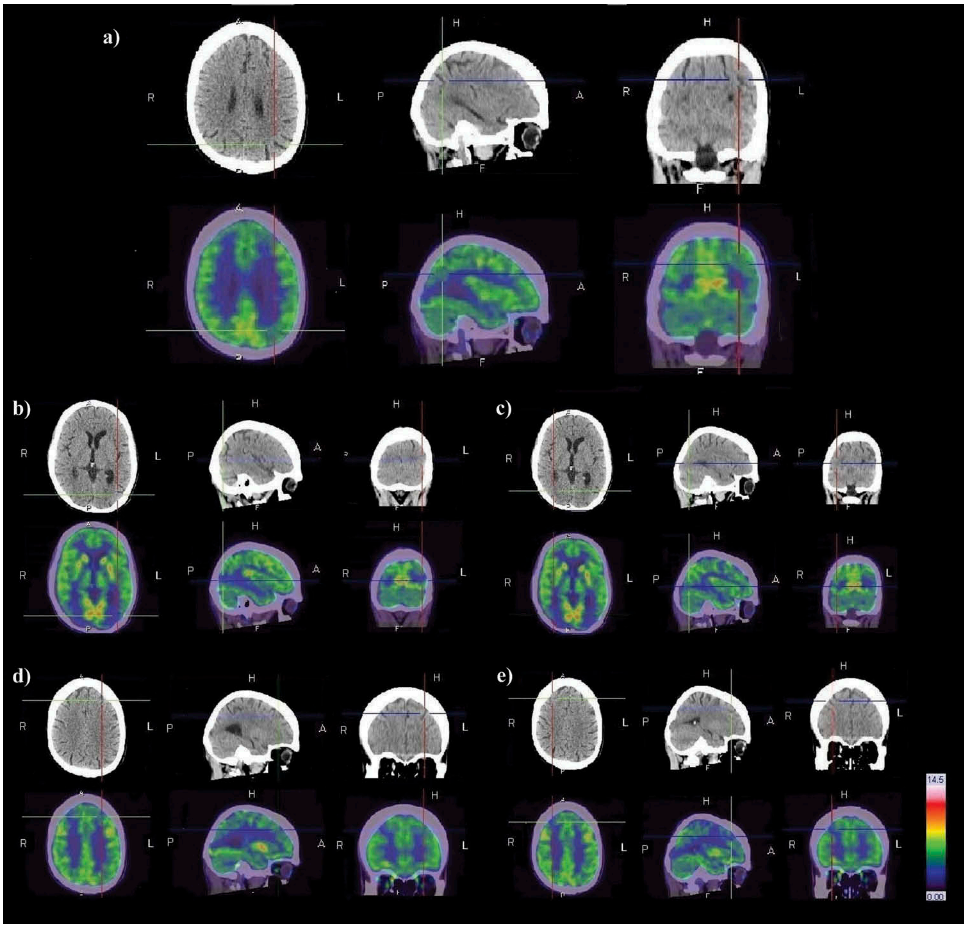

Figure 1. ^{18}F-fluorodeoxyglucose (FDG) brain positron emission tomography/computed tomography (PET/CT). The patient was asked to fast for at least 6 hours before the examination. The blood glucose level of the patient was determined before the examination. Scanning was not performed until the blood glucose level was less than 140 mg dL^{-1}. The test was performed using a hybrid PET/CT scanner (Siemens mCT Biograph, Germany). The brain CT scanning was performed using a continuous spiral technique on a 64-slice helical CT, and the PET scanner had three detector rings. No contrast medium was administered during CT scanning. After the CT scan, an emission scan was performed from the head to the thigh after the intravenous injection of 0.08 mC kg^{-1} (2.96 MBq kg^{-1}) FDG CT and PET scan data were coregistered. The standardized uptake value (SUV) was acquired using the attenuation-corrected images, the amount of injected FDG, the body weight of the patient, and the cross-calibration factors between PET and the dose calibrator. The images are displayed following the neurological standard (left to right side) and are based on an SUV scale (from red = activation to blue = no activation). Reduced metabolism is evident in: (a) temporoparietal areas, (b) left and (c) right parietal–occipital junctions; (d) left and (e) right frontal areas. To view a color version of this figure, please see the online issue of the Journal.

objects. Finally, hypometabolism was found in the right dorsolateral frontal cortex, which may explain M.R.'s impairment in planning tasks (FAB; Tower of London; Behavioural Assessment of the Dysexecutive Syndrome, BADS).

2. Experimental design: Cross-modal matching in the recognition of overlapping figures

A new experimental task was devised to investigate the potential influence of multisensory facilitation on the identification of multiple overlapping visual stimuli. First, a preliminary stimulus (cue) was presented in one of four sensory modalities: visual, tactile, auditory, or olfactory. Next, a stimulus consisting of two overlapping images was shown in visual modality, and M.R. was requested to identify and denominate both the objects shown in the overlapping images. Only in half of the overlapping images did the cue (valid cue) correspond to one of the two images (target), while in the other half there were no objects corresponding to the cue (invalid cue).

2.1. Stimuli

In order to ensure that the degree of difficulty was comparable in each of the conditions, all the stimuli were selected from the Birmingham Object Recognition Battery (BORB) subtests (Riddoch & Humphreys, 1993), with the exclusion of those that had been used during the neuropsychological assessment.

The visual cues were outlines of objects drawn in black (10.6 cm × 10.6 cm), and they were identical to the target stimulus in the overlapping figures in all but the rotation (see below). For the other nonvisual cues, real objects served as tactile stimuli (e.g., a comb, a balloon), natural sounds were played in the headphones as auditory cues (e.g., a bell, a match being struck), and real odors were used for the olfactory stimuli (e.g., an onion, a cigarette).

Each cue was followed by a stimulus showing two overlapping images, each image rotated 45 degrees in the opposite direction to the other image. These showed the cued object and the distractor images in the valid trials and two noncued objects in the invalid trials. The two objects in the overlapping figures were not perceptually or semantically related. Each overlapping stimulus was presented twice for each of the two rotation positions (see Figure 2).

Four separated lists of stimuli were created for the various sensory modalities (visual, n = 36; tactile, n = 24; auditory, n = 12; olfactory, n = 12; see Appendix Table A1). The stimuli in the four lists were each administered twice, for a total of 168 stimuli.

The number of trials for each modality was unbalanced because no more than six cues were available for the olfactory and auditory modalities.

An additional list of 24 different overlapping images without any cues (baseline and follow-up lists) was presented before and after the experimental procedure as a general measure of the ability to recognize overlapping images.

Three healthy subjects ($M \pm SD$, age = 39.66 ± 7.50 years; education and gender matched to M.R.) were recruited to verify whether the lists compared in terms of the degree of difficulty. Their accuracy and response time for denominating the two objects in the overlapping images were recorded and analyzed.

2.2. Procedure

M.R. sat approximately 55 cm away from a 15" LCD monitor (resolution 1024 × 768 pixels; refresh frequency 60 Hz). After observing a central fixation point (1000 ms), a cue (visual or nonvisual: auditory, tactile, or olfactory) appeared for 3000 ms. A black-and-white random-dot mask (10.6 cm × 10.6 cm in size, duration 500 ms) was then shown, followed by the overlapping image stimulus, which remained until the subject responded (Figure 2a). Crucially, in half of the trials (n = 84), the cues were valid and consistent with one of the objects (target) shown in the overlapping images, while the other image represented a different (nontarget) object. In the other half of the trials both the objects in the overlapping images were nontarget—that is, different from the cue (invalid cue).

M.R. was requested first of all to click the computer mouse in order to indicate whether or not the overlapping images included the previous administered cue (*identification task*, response: Yes/No). He used his right hand to click the left key for Yes and the right key for No. The patient was then asked to denominate both the objects represented in the overlapping images stimulus (*denomination task).*

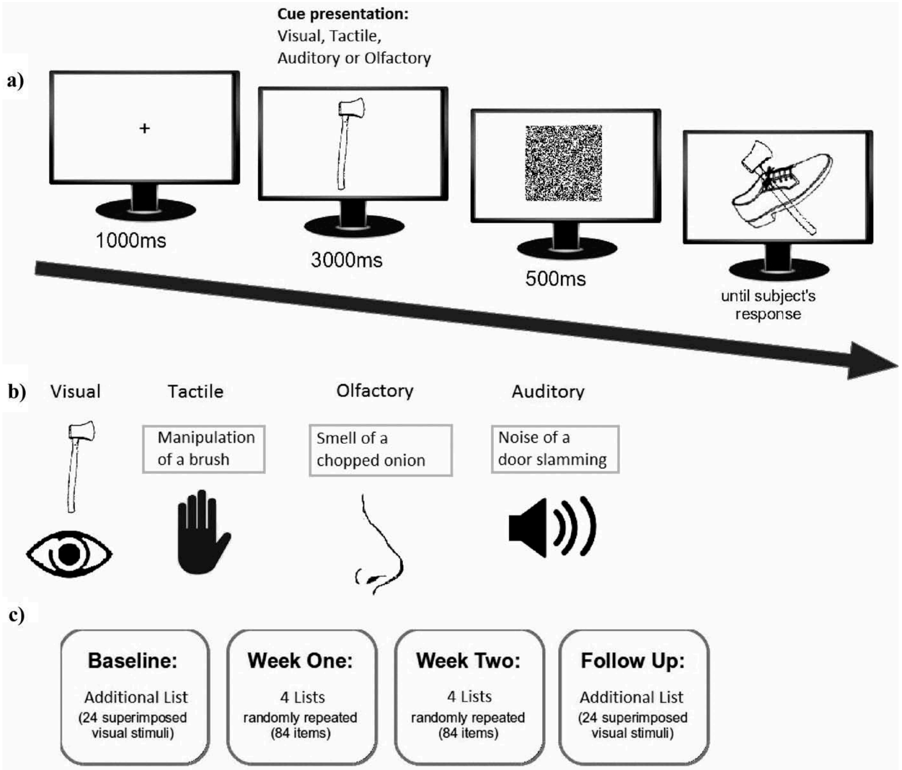

Figure 2. The experimental task. (a) Timeline regarding the procedure for each individual item. (b) Examples of sensory primes used in the four conditions. (c) The general timeline of the experiment.

In the baseline list, there were no cues, and the central fixation point (1000 ms) was followed by an overlapping image showing two objects, which remained until M.R. had denominated them.

Accuracy in the identification task was automatically recorded by the software, while in the denomination task an examiner manually annotated M.R.'s answers.

The four experimental lists were randomly repeated in two consecutive sessions, with an interval of a week between the sessions (total = 168 items). The additional baseline list was presented before (baseline) and after (follow-up) the whole experimental procedure.

E-prime 2.1 software (Psychology Software Tool Inc., Pittsburgh, PA) was used to control timing and randomization.

2.3. Statistical analyses

The trials where M.R. failed to recognize the cue were excluded from the analyses (7 out of 168).

For the identification task, in order to test whether there were differences in accuracy between the various conditions, a 4 × 2 log–linear model was computed with sensory modality (visual, tactile, olfactory, auditory) and answer (correct, error) as factors.

To ascertain whether the presence of the cue in the denomination task facilitated M.R.'s recognition of both the target and nontarget stimuli, his responses were analyzed by means of log–linear models. For each sensory modality, the frequency of valid-cued and invalid-cued items were compared in a 2 (cue: valid, invalid) × 3 (response: 0, 1, 2) log–linear model. In this way, the benefit of the cue was recorded when the two-way Cue × Response interaction was significant, in particular when the frequency of Type 2 responses in the valid-cued trials was greater than that in the invalid-cued trials.

In order to specifically analyze the frequency of each response type (0, 1, 2) for each modality in the valid-cued and invalid-cued trials, post hoc analyses were then computed with χ^2 tests, all false discovery rates (FDRs) corrected (Benjamini & Hochberg, 1995). In all of these comparisons, Cramer's V effect size was adopted ($V < 0.1$ = negligible effect, $0.1 \leq V < 0.2$ = weak effect, $0.2 \leq V < 0.4$ = moderate effect,

$0.4 \leq V < 0.6$ = relatively strong effect, $0.6 \leq V < 0.8$ = strong effect, and $0.8 \leq V \leq 1$ = very strong effect; Rea & Parker, 1992).

Furthermore, M.R.'s performance at the baseline was tested against his performance with the valid-cued items and with the invalid-cued items. This comparison was necessary in order to understand whether a valid cue had a facilitating effect by itself, or whether it was the invalid cue that impaired performance. Therefore, two log–linear models were computed with the following factors: condition (baseline vs. valid-cued items and baseline vs. invalid-cued items, respectively) and response (0, 1, 2).

In the case of a facilitating effect due to the cue, the two-way interaction (Condition × Responses) should be significant in the first model (with higher frequencies for Type 2 responses in the valid-cued trials than in the baseline). In addition, the exclusion of a negative, inhibitory effect due to an invalid cue would be confirmed by the absence of a significant interaction in the second model.

Finally, to verify any potential effects of general improvement, the baseline and follow-up lists were compared in a 2 (time: baseline vs. follow-up) × 3 (response: 0, 1, 2) log–linear model.

3. Results

The performance of the controls confirmed that the stimuli lists were balanced for difficulty. No differences between the lists in terms of accuracy, $\chi^2(2) = 3.831$, $p > .05$, or response times, $F(1, 4) = 0.919$, $p > .05$, were found (general accuracy in denomination of overlapping figures = 94.59%, range = 200–209/216).

3.1. Identification task

In this task, M.R.'s rate of accuracy was 93.17% overall (*M* ± *SD*: 92.62 ± 5.52 across lists). He failed to identify 7 (11.27%) valid cues in the overlapping images, and there were only 3 (4.83%) false alarms (i.e., when he indicated a cue that was not shown in the target). An accuracy analysis showed no significant effects for modality, $\chi^2(3) = 4.262$, $p = .234$, answer, $\chi^2(1) = 2.972$, $p = .085$, or Modality × Answer interaction, $\chi^2(3) = 2.344$, $p = .504$.

3.2. Denomination task

Results indicated that the cue enhanced M.R.'s performance, although to different degrees depending on the sensory modality (Figure 3 and Table 4).

The *visual cue* significantly improved M.R.'s performance. We found significant effects of cue, $\chi^2(1) = 12.395$, $p < .001$, response, $\chi^2(2) = 18.418$, $p < .001$, and the Cue × Response interaction, $\chi^2(2) = 16.305$, $p < .001$. Direct χ^2 analyses showed that there were more Type 2 responses, $\chi^2(1) = 4.556$, $p = .049$, $V = 0.251$, and fewer Type 0 responses, $\chi^2(1) = 12.518$, $p = .001$, $V = 0.417$, in valid-cued trials than in invalid-cued trials. No significant effect was found for Type 1 responses, $\chi^2(1) = 0.589$, $p = .442$, $V = 0.121$.

The effect of valid cues was also confirmed in the Condition × Response interaction, $\chi^2(2) = 10.264$, $p = .006$, in the comparison between valid-cued trials and the baseline [no effects of condition, $\chi^2(1) = 2.093$, $p = .148$, or response, $\chi^2(2) = 4.471$, $p = .107$]. Direct χ^2 analyses showed that there were more Type 2 responses in the visual valid-cued trials in the baseline, $\chi^2(2) = 6.790$, $p = .027$, $V = 0.336$. No significant effects were found for either Type 1 or Type 0 responses [$\chi^2(1) = 3.179$, $p = .112$, $V = 0.28$; $\chi^2(1) = 1.247$, $p = .2641$, $V = 0.18$].

Finally, in the comparison between invalid-cued visual trials and the baseline there was a main effect of condition, $\chi^2(1) = 4.717$, $p = .030$, with invalid trials worse than baseline (see Table 4), but no other effects [response: $\chi^2(2) = 4.471$, $p = .107$; Condition × Response interaction: $\chi^2(2) = 5.338$, $p = .069$].

The *tactile cue* also significantly improved M.R.'s performance. A comparison showed significant effects of cue, $\chi^2(1) = 10.971$, $p < .001$, and response, $\chi^2(2) = 12.293$, $p = .002$, and the Cue × Response interaction, $\chi^2(2) = 14.509$, $p < .001$. In a direct comparison between valid and invalid-cued trials, Type 0 responses were significantly fewer for valid-cued stimuli, $\chi^2(1) = 10.206$, $p = .004$, $V = 0.476$. Although there were no other direct differences, the sum of Type 1 and 2 responses was higher for valid-cued than for invalid-cued trials, $\chi^2(1) = 10.206$, $p = .001$, Cramer's $V = 0.476$.

The comparison between valid-cued trials and the baseline showed a main effect of condition, $\chi^2(1) = 3.962$, $p = .046$, with tactile better than

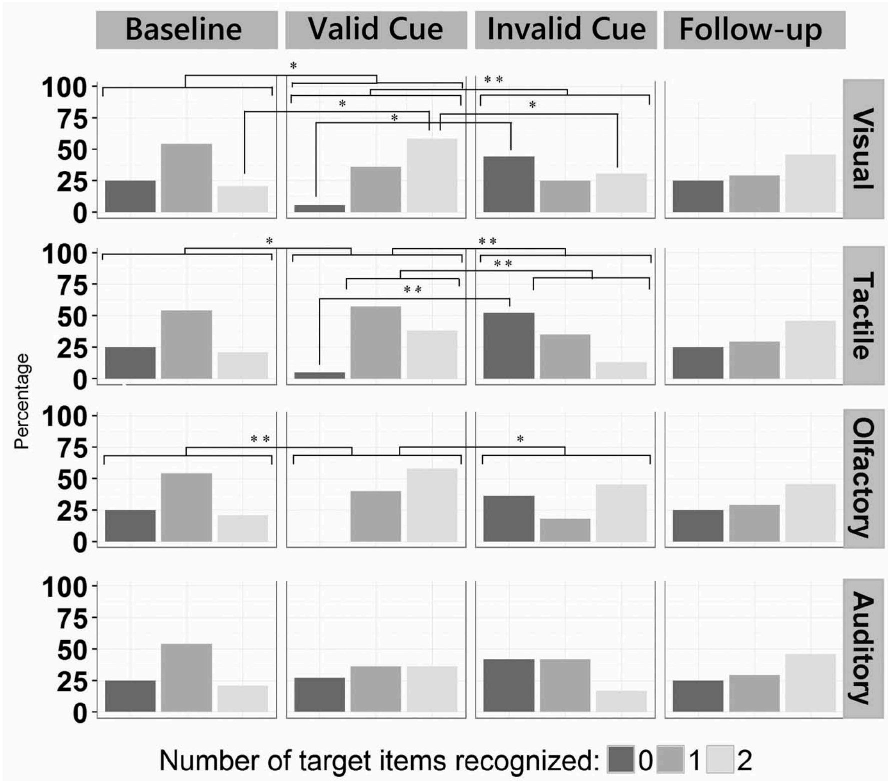

Figure 3. M.R.'s results in the experimental task. For each cue modality (as shown on the right) the frequency of responses in the valid-cued condition (second column) is compared with that in the baseline (left column) and the invalid-cued condition (third column). The follow-up condition (right column) is compared with the baseline condition. (Baseline and follow-up on the additional list: See text.) *$p < .05$. **$p < .01$.

Table 4. Table of frequencies in percentages, divided by conditions, responses, and cues.

	Baseline			Typology of cue			Follow-up		
Cue	0	1	2	0 Valid–invalid	1 Valid–invalid	2 Valid–invalid	0	1	2
Visual	25	54.17	20.83	5.56–4.44***	36.11–25	58.33–0.56*,[b]			
Tactile				4.76–52.17**	57.14–34.78[a]	38.1–13.04[a]	25	29.17	45.83
Olfactory				0–36.36	45.45–18.18	54.55–45.45			
Auditory				27.2–41.67	36.36–41.67	36.36–16.67			

[a]Valid Cued Response 1 + Response 2 versus Invalid Cued Response 1 + Response 2, $p < .001$; [b]Valid cued items versus baseline, $p < .05$. *Valid versus invalid cue, $p < .05$; **Valid versus invalid cue, $p < .01$; ***Valid versus invalid cue, $p < .001$.

baseline (see Table 4), but no effects for response, $\chi^2(2) = 4.4710$, $p = .107$, or for the Condition × Response interaction, $\chi^2(2) = 4.501$, $p = .105$. Finally a comparison between invalid-cued tactile trials and the baseline did not reveal any differences [condition: $\chi^2(1) = 2.039$, $p = .153$; response: $\chi^2(2) = 4.471$, $p = .107$; Condition × Response interaction: $\chi^2(2) = 3.725$, $p = .155$].

The *olfactory cue* significantly improved denomination in valid-cued trials in comparison to invalid-cued trials. We found main effects of cue, $\chi^2(1) = 5.545$, $p = .018$, response, $\chi^2(2) = 8.512$, $p = .014$, and the Cue × Response interaction, $\chi^2(2) = 6.268$, $p = .043$. No differences between valid and invalid-cued trials were found in direct χ^2 contrasts.

Nevertheless, denomination after olfactory valid cues was significantly better than at baseline as indicated by the main effect of condition, $\chi^2(1) = 8.317$, $p = .004$, and the Condition × Response interaction, $\chi^2(2) = 7.486$, $p = .024$, but with no effect of response, $\chi^2(2) = 4.471$, $p = .107$. Direct χ^2 did not show any significant effects.

Finally a comparison between invalid-cued trials and baseline indicated that there were no differences [condition: $\chi^2(1) = 0.403$, $p = .526$; response: $\chi^2(2) = 4.471$, $p = .107$; Condition × Response interaction: $\chi^2(2) = 4.471$, $p = .107$].

In the denomination task no specific advantage of the *auditory* valid cue was found [cue: $\chi^2(1) = 0.505$, $p = .477$; responses: $\chi^2(1) = 0.188$, $p = .91$; Cue × Response interaction: $\chi^2(2) = 1.253$, $p = .534$]. Furthermore, there were no differences either between valid-cued trials and the baseline [Condition: $\chi^2(1) = 1.019$, $p = .313$; Response: $\chi^2(1) = 4.471$, $p = .107$: Condition × Response interaction: $\chi^2(2) = 1.201$, $p = .548$] or between invalid-cued trials versus the baseline [$\chi^2(1) = 0.091$, $p = .762$; response: $\chi^2(2) = 4.471$, $p = .107$; Condition × Response interaction: $\chi^2(2) = 1.025$, $p = .599$].

3.3. Baseline and follow-up lists

A comparison between the baseline and the follow-up lists did not show any significant differences [time: $\chi^2(1) < 0.001$, $p \approx 1.00$; response: $\chi^2(2) = 4.471$, $p = .107$; Time × Response: $\chi^2(2) = 4.134$, $p = .127$].

4. Discussion

In this study the potential effects of different types of sensory cue in terms of reducing simultanagnosia were investigated in a patient with Balint's syndrome. The diagnosis was formulated based on the results from a detailed neuropsychological assessment and was supported by an accurate analysis of underlying lesions by means of a ^{18}F-FDG Brain PET/CT. This double imaging method (PET/CT) provided a valid support for the identification of functional damage. In effect, it is well known that damage resulting from anoxic aetiology generally causes multifocal lesions and areas of hypodensity that are not easy to identify with traditional neuroimaging techniques.

Our experimental results show that the ability to recognize overlapping pictures may be improved by presenting a valid cue prior to the task, not only using the same (i.e., visual) modality but also using other sensory modalities. Crucially, the sensory cue improved performance not only for the target object, but also for the nontarget object. This suggests that the effect produced by the presentation of a cue acts on the visual system, allowing the patient to disambiguate the two overlapping images and thus separate them. Indeed, while M. R. was able to identify the (cued) target as he recognized it from the previous equivalent cue, his improvement in terms of recognition of non-target objects can only be due to the fact that he visually recognized the overlapping objects in the image. In addition, the fact that there were very few false alarms (i.e., the trials with an invalid cue where the patient incorrectly indicated the cue as an object present in the stimulus) rules out the possibility that M.R. was basing his responses exclusively on his previous recognition of the cue.

4.1. Balint's syndrome

The patient here described showed certain specific signs of BS. The initial symptoms of neglect had totally disappeared by the time of the experimental study, and M.R. did not suffer from visual acuity or serious visual field deficits. Ocular apraxia had been present exclusively in the acute phase when M.R. was totally unable to voluntarily move his gaze, which appeared fixed and vacuous (the "psychic paralysis of gaze" originally described by Bálint, 1909). At the time of our assessment, his inability to compare object size or lengths remained, probably at least in part due to simultanagnosia. M.R. was able to grasp moving objects but failed to point at or grasp unmoving objects or pick out one object from among others (optic ataxia).

As previously described in other cases (Chechlacz & Humphreys, 2014; Dalrymple, Barton, & Kingstone, 2013), the most evident symptom manifested by M.R. was certainly simultanagnosia (i.e., his inability to interpret complex visual displays due to a difficulty in processing multiple items and the relations between them; Wolpert, 1924). M.R. complained that he saw a chaotic and incoherent picture of the surrounding world, and this was confirmed by the assessment that showed that he was unable to see more than one object, or even a piece of an object, at a time. He appeared to be totally unaware that what he was looking at was only part of a larger image, and he was unable to synthesize the elements of a scene in order to produce the overall scene (Rafal, 2001). Although M.R.'s symptoms were compatible with both the dorsal and the ventral forms of simultanagnosia (Farah, 1990), we consider that he mainly suffered from object-based disorders. Indeed, he could identify multiple objects in space (although slowly), and he did not present with spatial or topographic deficits. In contrast he failed to identify multipart, complex, overlapping objects, even when these occupied the same spatial coordinates as an object that he could see (Rafal, 2001). Our patient's symptoms do not seem to be totally consistent with the theories that have been advanced to explain simultanagnosia. The "restriction of visual attention hypothesis" suggests that simultanagnosia consists of an isolated inability to focus patients' attention across a wider area (Rafal, 2003; Rizzo & Vecera, 2002).

Moreover, M.R.'s symptoms only in part support the "integrated competition hypothesis" (Duncan, Humphreys, & Ward, 1997), which explains simultanagnosia as the result of an all or nothing competition between objects (Jackson, Swainson, Mort, Husain, & Jackson, 2009). In fact, he recognized only one element at a time in complex scenes and omitted (or neglected) the others. Nevertheless, following this theory, the patient would be expected to systematically recognize one of the two overlapping images, while in the baseline and the nonfacilitated condition, M.R. failed to identify either of the two objects represented in the stimuli.

Rather than an isolated attentional problem, we propose that M.R.'s disorders involve an interaction mechanism between spatial attention and processes of perceptive grouping (Chica, Bartolomeo, & Valero-Cabré, 2011; Shalev, Humphreys, & Mevorach, 2004). This interpretation is confirmed by experimental data that have shown that the features of a stimulus can modify the expression of simultanagnosia, for example the distance between local elements in compound forms (Dalrymple, Kingstone, & Barton, 2007; Huberle & Karnath, 2006; Montoro, Luna, & Humphreys, 2011), as can the significance of a stimulus or its familiarity (Coslett & Saffran, 1991; Shalev, Mevorach, & Humphreys, 2007). In addition, the salience of a stimulus may influence the symptoms (Dalrymple et al., 2007; Montoro et al., 2011).

Mevorach and colleagues (2014) found that manipulating local and global shapes, so that either the former or the latter were salient, changed the patient's performance, showing an effect of local or global "capture," which was simply dependent on the relative salience of the shape. This capture effect may also be associated with an inability to disengage the focus of attention from a stimulus (Farah, 1990).

In effect, it is probably impossible to identify one single disorder underlying simultanagnosia due to variability in the symptoms as a result of different aetiologies and the co-occurrence of other deficits. Discordant findings probably reflect the existence of distinct subtypes (Coslett & Lie, 2008) associated with at least partially different lesions.

Disorders in recognizing a whole object are reported even in integrative visual agnosia (Humphreys & Riddoch, 1987). This is a particular type of apperceptive visual agnosia involving deficits related to recognizing single objects, but preserved abilities in the analysis of their single parts. We exclude this possibility as M.R. showed spared abilities in processing individual drawings and real objects. Furthermore, integrative agnosia is reported after lesions in the bilateral posterior and ventro-medial occipital-temporal areas, including the inferior temporal, fusiform, and lingual gyri (Riddoch et al., 2008).These ventral areas were spared in M.R. Nevertheless, we cannot completely exclude the presence of signs of visual agnosia in M.R., as his scores in some of the BORB tasks were at or below cutoff.

4.2. Facilitation effects induced by a visual cue

Our results indicate that a visual cue helped M.R. to discriminate the elements in two overlapping figures. Crucially, when the stimuli were cued this increased his ability to recognize not only the target but also the not-target stimuli. In other words, when the patient was able to match the cue with the target in the overlapping figures (identification task) and to identify one object in the double stimulus (denomination task), he was then also able to separate this object perceptively from the other object and to distinguish each of these as one single object.

This is probably due to an integration of different mechanisms, linked to both bottom-up and top-down processes.

The cue presented in the same visual modality as the target in the overlapping figure may have activated an implicit mechanism of perceptive priming (Brunel, Carvalho, & Goldstone, 2015). In this way, the valid cue not only increased the likelihood of M. R. being able to discriminate the primed target, but also reduced the complexity of the overlapping figures. In fact, a sort of "pop-out" effect of the valid-cued stimulus allowed the patient to segregate the two images in the overlapping figures.

An "enlargement of the attentional window" effect (Shavel, Humphreys, Mevorach, 2004) produced by means of a priming task (with a procedure similar to ours and a delay between the stimuli) was suggested in a single-case study involving a patient affected by BS (Shavel et al., 2004). There was an improvement in the patient's ability to visually recognize compound letters following a preliminary task in which he had been asked to identify one of the same letters.

A similar process has also been reported in the literature on simultanagnosia as the effect of "familiarity" (Shalev, Mevorach, Humphreys, 2007). In an interesting study, Shalev et al. (2007) demonstrated that their patient perceived only the global shape of a compound letter when its local elements were unfamiliar; however, after the patient was trained to identify the local (previously unfamiliar) elements, it became difficult for him to perceive global forms containing the now familiar local elements. Thus, familiarity changed the salience of the stimulus.

With regard to potential bottom-up mechanisms, we finally considered the possibility that the valid cue facilitated a disengagement of attention from the global stimulus ("global capture," Mevorach et al., 2013), allowing M.R. to identify the two separate figures. In other words, cues potentially represent an instrument that allows the patient to overcome the global capture effect. One of our results at least partially supports this assumption: In the trials with an invalid cue in the denomination task (i.e., when the cue was not the same as one of the objects in the overlapping images), M.R.'s performance worsened significantly in comparison to the baseline.

However, we suggest that also top-down, semantic memory processes were involved in our experimental results. Previous results support this interpretation. In a single-case study, Coslett and Saffran (1991) found that their patient was better at identifying two simultaneously presented words when these were components of compound words (e.g., BASE and BALL) or were semantically related (e.g., HOT and COLD) than when they were unrelated. Better recognition was also found for pairs of line drawings that were semantically related (e.g., both animals) than for those that were unrelated (e.g., an animal and a tool; Coslett & Saffran, 1991). Thus, previous semantic knowledge activated by the cue may play a role in increasing the ability to recognize the objects in overlapping figures.

That said, we suggest that the improvement in performance induced by visual cues was not due specifically either to the visuospatial perceptive (priming/familiarity) or to attentional (disengagement) or semantic systems, but rather to the integration of these bottom-up and top-down processes.

4.3. Cross-modal effects on the perception of overlapping images

In everyday situations, people perceive the surrounding complex environment as a unique, coherent whole, thanks to the integration of multiple sensory systems such as the olfactory, auditory, visual, gustatory, and tactile systems. The likelihood and speed of detection and identification of events is higher when inputs come from two or more sensory channels than when they come from only one (Demattè, Sanabria, & Spence, 2006, 2009; Gottfried & Dolan, 2003; but see also Marini, Chelazzi, & Maravita, 2013, for eventual opposite effects).

Cross-modal integration is certainly supported by neuronal networks at multiple levels. A first level acts relatively early in subcortical brain structures (e.g., the colliculus) and in the primary sensory cortices. Here, there are bimodal neurons that at the same moment respond to stimuli presented in two different modalities, in particular when those two stimuli occur in close spatial and temporal proximity (Diaconescu, Hasher, & McIntosh, 2013; Fort et al., 2002; Gottfried & Dolan, 2003). A second step involves the associative cortices. For example, synchronous auditory–tactile stimulation induces cross-modal facilitation effects and increases the auditory intensity rating thanks to the auditory–tactile multisensory neurons in the auditory associative cortex (Gillmeister & Eimer, 2007). In addition to these sensory areas, multisensory integration in humans is supported by a complex, widespread network. This involves the superior temporal sulcus, which is associated with the integration and labelling of objects, and the intraparietal sulcus, involved in spatial information processing (Calvert, 2001; Stein & Stanford, 2008). In these areas an overlapping activation related to three different senses (tactile, auditory, and visual) has been recorded (Beauchamp, Yasar, Frye, & Ro, 2008; Bremmer et al., 2001; Langner et al., 2012). Furthermore, the retromedial orbitofrontal cortex and hippocampal areas have been identified as neuronal correlates of multisensory integration involving the olfactory and gustatory domains (Gottfried & Dolan, 2003; Price, 2008). As M.R. had suffered from an anoxic (not focal) damage, there is the real possibility that all these stages of the process are in some way affected. Unfortunately, our experimental design does not allow us to specifically identify the type of multisensory interactions that drive the effects found.

In contrast to the case of visual cues, we consider that the multisensory integration/summation effects in our experiment are mainly due to top-down high cognitive functions such as the endogenous orientation of attention and semantic memory (Rizzo & Vecera, 2002). For this reason, our patient's improvement with nonvisual cues probably made use of widespread neural networks.

However, M.R.'s ability to recognize both cued and noncued objects in the overlapping figures improved. The only explanation for this is that the top-down factors impacted on visual processing. Thus, we suggest that the semantic mental representations and short-term memory (Shinn-Cunningham, 2008) activated by the cue produced a segregation effect for the cued object (similar to the effects induced by priming and familiarity in visual modality), with a further "pop-out" mechanism that enabled the patient to disambiguate the overlapping figures and identify the second stimulus.

Another possible interpretation of our results refers to the top-down effects of expectation relating to imminent stimuli, which may have mediated a specific endogenous re-orientation of attention towards the individual objects in the overlapping figures. When sensory stimuli occur close together in time and space, they are more likely to be expected by individuals to be associated signals coming from a common source ("top-down expectation"; Gau & Noppeney, 2016; Körding et al., 2007; Magnotti, Ma, & Beauchamp, 2013). In our task, immediately after exploring the cue, the patient may have been in an expectation condition, awaiting the presentation of the same object, which would as a result be more easily detected. However, the expectation effect alone does not explain the improvement in performance relating to M.R.'s recognition of the second noncued stimulus in the overlapping images. In addition, it is important to consider that the patient was aware that the cue might or might not anticipate one of the objects shown in the overlapping images (50% of the probability). This probably reduced the expectation effect to some extent.

In conclusion, we consider that identifying a previous stimulus influenced M.R.'s capacity to perceive overlapping objects, probably due in part to different factors in the visual and cross-modal conditions. We suggest that a combination of bottom-up (priming, familiarity, attention disengagement) and top-down (orientation of attention, expectation, semantic memory) processes came into play when the cue was visual, while top-down mechanisms acted in the integration of inputs in cross-modal cues.

It is worth noting that integration with cross-modal cues was not as efficacious as visual facilitation in terms of reducing simultanagnosia, and neither did the auditory modality have any notable effects. Various different factors may explain this result. The visual cue was perceptively identical (although not rotated through 45° like the target stimuli) and for this reason represented the most salient cue. In contrast, nonvisual cues only matched the target stimuli semantically. In addition, while the temporal proximity between cue and target was identical for all of the modalities, spatial congruency was only respected in the visual modality (Frassinetti, Bolognini, & Làdavas, 2002; Valenza et al., 2004).

While the tactile and olfactory cues were efficacious in improving M.R.'s recognition of overlapping objects, the auditory cues did not have any influence. A possible explanation is that the acoustic cues were too difficult to identify and thus did not provide useful information. In fact, M.R. made many mistakes in recognizing acoustic cues (33.33% errors: 1 error and 3 missed in the *identification* task).

Unfortunately, the effects of experimental manipulation were only temporary and were not generalized to other stimuli, as demonstrated by the fact that there were no differences in M.R.'s scores for the additional list administered before and after the experimental procedure. Thus, in terms of recovery, cross-modal integration does not seem to represent a useful strategy for rehabilitation. Nevertheless, the number of trials for each modality used in our experiment are probably too few to induce any long-term changes. Only more specific, prolonged programs will indicate the potential effects of cross-modal facilitation in simultanagnosia.

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Appendix

The four lists of the pairs in the overlapping images, divided on the basis of the modality of the related cues (visual, tactile, olfactory, and auditory). The valid cued are in bold. During the experiment the lists were repeated twice.

Table A1.

Visual cues	
Bee	Screw
Fish	Vest
Clown	Rolling pin
Skunk	**Arrow**
Toothbrush	Church
Tiger	Stairway
Cauliflower	Tennis racket
Spiderweb	Moon
Candle	Leg
Pyramid	Toaster
Television	Bottle
Whistle	Spider
Balloon	Crutch
Leopard	Switch
Doll	Star
Iron	Earring
Pepper	Zebra
Donkey	**Tie**
Peanut	Sled
Mill	Box
Boot	Phone
Bolt	Bowl
Stool	Pot
Chisel	Rugby ball
Broom	Tree
Kite	Grasshopper
Wheelbarrow	**Cigarette**
Ball	Beetle
Axe	Shoe
Pyramid	Toaster
Ring	Desk
Lamp	Snowman
Heart	Scraper
Knob	Baseball bat
Belt	Carafe
Comb	Fridge

Tactile cues	
Potatoes	Spinning top
Squirrel	Suitcase
Anchor	Helmet
Caterpillar	**Basket**
Reel	Elephant
Spoon	Watering can
Crown	Asparagus
Necklace	Penguin
Button	Harp
Swan	Egg
Dromedary	Window
Ant	Ink
Balloon	Crutch
Leopard	Switch
Toothbrush	Church
Doll	Star
Kite	Grasshopper
Pepper	Zebra
Ring	Desk
Lamp	Snowman
Heart	Scraper
Knob	Mace
Belt	Carafe
Comb	Fridge

Olfactory cues	
Cauliflower	Tennis racket
Spiderweb	Moon
Candle	Leg
Broom	Tree
Iron	Ear
Wheelbarrow	**Cigarette**
Flower	Sail boat
Ironing Board	Nose
Salt shaker	Seal
Bike	**Onion**
Seahorse	**Ashtray**
Lobster	Bread

Auditory cues	
Bow	Sun
Cake	Cloud
Match	Skate
Ball	Cockroach
Axe	Shoe
Pyramid	Toaster
Television	Bottle
Whistle	Spider
Bell	Gorilla
House	Goal
Circus	Pen
Moscow	Corkscrew