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# Functional Neuroanatomy of Blindsight Revealed by Activation Likelihood Estimation Meta-analysis

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**ABSTRACT**

Blindsight, the residual abilities of patients with cortical blindness to respond proficiently to stimuli they do not consciously acknowledge, offers a unique opportunity to study the functional and anatomical mechanisms sustaining visual awareness. Over decades, the phenomenon has been documented in a wide number of different patients, across independent laboratories, and for a variety of tasks and stimulus properties. Nevertheless, the functional neuroanatomy of blindsight remains elusive and alternative proposals have been put forth. To tackle this issue from a novel perspective, we performed a quantitative Activation Likelihood Estimation (ALE) meta-analysis on the neuroimaging literature available on blindsight. Significant activity was reported in subcortical structures, such as the superior colliculus, pulvinar and amygdala, as well as in cortical extrastriate areas along the dorsal and ventral visual stream. This data-driven functional network collectively defines the extant neural fingerprint of blindsight. To further characterize the unique combination of segregation and integration in brain networks engaged in blindsight, we measured the relationship between active areas and experimental features in the original studies, their clustering and hierarchical organization. Results support a network-based organization in the functional neuroanatomy of blindsight, which likely reflects the intersection of different stimulus properties and behavioural tasks examined. We suggest that the conceptualization of blindsight as a constellation of multiple nonconscious visual abilities is better apt as a summary of present-day wisdom, thereby mirroring the variety of existing V1-independent pathway and their different functional roles.

*Keywords:*

Blindsight, Meta-analysis, Activation Likelihood Estimation, Hierarchical Clustering, fMRI, Visual awareness, NCC

## 1. Introduction

According to the Oxford Concise Dictionary, “*blindsight*” refers to “a condition in which the sufferer responds to visual stimuli without consciously perceiving them”. The “sufferer” in the definition denotes a patient with damage to the occipital lobe, more precisely to the primary visual cortex (V1), which leads to clinical blindness in the corresponding (contralesional) visual field. Its eponymous discoverer, Larry Weiskrantz, introduced the term as a light-hearted title for a seminar in Oxford more than 40 years ago, and the first use of the word in print can be found in a brief report published on *Lancet* in 1974 (Sanders, Warrington, Marshall, & Weiskrantz, 1974). Initial independent observations on retained visual abilities in the absence of awareness were reported in the same years (Perenin, 1978; Perenin & Jeannerod, 1975, 1978; Pöppel, Held, & Frost, 1973; Weiskrantz, Warrington, Sanders, & Marshall, 1974). However, unsystematic observations of similar phenomena in monkeys date back to more than a century ago in writings of the Italian physiologist Luigi Luciani (1884), and in the works of pioneering neurologists such as Poppelreuter (1917), Riddoch (1917), and Teuber (1960). As an historical exercise, the same oxymoron was used by Shakespeare in *Richard III*, when the Duchess of York reports her miserable condition by stating: “Dead life, blind sight, poor mortal living ghost”.

As one of the main goals in neuroscience is to characterize the relationship between neural structures and their functions, blindsight offers an invaluable opportunity to shed light on the role of the multiple visual pathways that bypass V1, and whose properties in the intact brain can be overshadowed by the canonical retino-geniculostriate pathway. There is an ever-growing list of spared abilities and residual functions documented in blindsight patients across a variety of methods. A not exhaustive list includes detection and spatial localization of stationary stimuli, motion sensitivity, line orientation, form and wavelength discrimination, semantic priming, and processing of emotional stimuli (for recent

reviews of these different aspects see Ajina & Bridge, 2016; Celeghin, de Gelder, & Tamietto, 2015; Cowey, 2004; Tamietto & Morrone, 2016; Weiskrantz, 2009). This plethora of nonconscious capacities has led to the emergence of different taxonomies based on distinct types of residual behaviours (Danckert & Rossetti, 2005), methods to gauge them (e.g., direct guessing vs. indirect methods) (Marzi, Minelli, & Savazzi, 2004), characteristics of the stimuli processed (e.g., affective blindsight, visuo-motor blindsight), or varying degrees of awareness reported (e.g. Type I vs. Type II blindsight) (Weiskrantz, 1998). Although each of these classifications holds value and warrants reference to the underlying neural structures possibly associated with different forms of blindsight, their capacity to address neural specificities “*is necessarily speculative*” (Danckert & Rossetti, 2005), and the structure-function relationship proposed remains inherently qualitative.

Functional magnetic resonance imaging (fMRI) studies on blindsight patients are making great strides in uncovering the neural structures that respond to stimuli projected in the blind field and that are associated with different nonconscious abilities. While in-depth investigation of selected cases remains the gold standard to sample the neural architecture of specific blindsight functions, there are inevitable limitations to the conclusions that can be drawn from individual reports. For example, most fMRI experiments are single-case studies and focus on specific stimulus properties and task demands. Additional variability is intrinsic in the different aetiologies, lesion onsets and extensions, and make it difficult to perform direct comparisons with similar studies beyond qualitative analogies.

Meta-analytic methods offer a valuable tool to synthesize quantitatively the functional neuroanatomy of a given phenomenon, either physiologic or pathologic, in a common space and beyond idiosyncrasies of individual studies (Laird, Lancaster, & Fox, 2005). Traditionally, indeed, meta-analyses describe only common activations across all studies considered, in order to remove from results any dependency from specific experimental setups. This approach can be useful to delineate the

“common neural space” of blindsight; that is, a set of areas that are significantly active during nonconscious perception, beyond specific attributes in the stimuli, tasks, and patients under investigation. However, a better understanding of the functional architecture of blindsight requires also quantification of unique mixture of plasticity and stability that characterizes the phenomenon. Reintroducing this specificity would thus allow to appreciate both segregation and integration of different nonconscious functions and their neural underpinnings (Shadish, Rindskopf, & Hedges, 2008). Actually, the unique contribution of each neural structure as a function of different tasks, or in relation to varying stimulus attributes reported in the original studies, can be retrieved from metadata and measured. In fact, it is possible to link every brain coordinate with information about how the observed activation was experimentally derived. Consequently, data-driven taxonomies and further clustering of functional subsystems can be derived from meta-analytic investigations. To our knowledge, however, a meta-analysis examining the neural bases of blindsight, their common properties and specificities, has never been performed thus far.

The present study makes a first step in this direction and, more in general, along the quest to characterize the broad spectrum of brain activity associated with multiple manifestations of nonconscious visual perception; an issue that has proven to be deceptively difficult to address. We have considered the entire fMRI literature available on blindsight. The focus of our investigation has been specifically on neural activity reported in response to stimuli presented in the blind field, and for which nonconscious visual abilities had been demonstrated. These fMRI data have been subjected to the Activation Likelihood Estimation (ALE) method, which is arguably best-suited for assessing the relationships between blindsight functions and regional brain activations (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Laird, Lancaster, et al., 2005). In fact, relevant neuroimaging studies are examined in the context of their unique experimental conditions. Three-dimensional coordinates or foci, corresponding to activation maxima for individual comparisons originally reported by each study, are

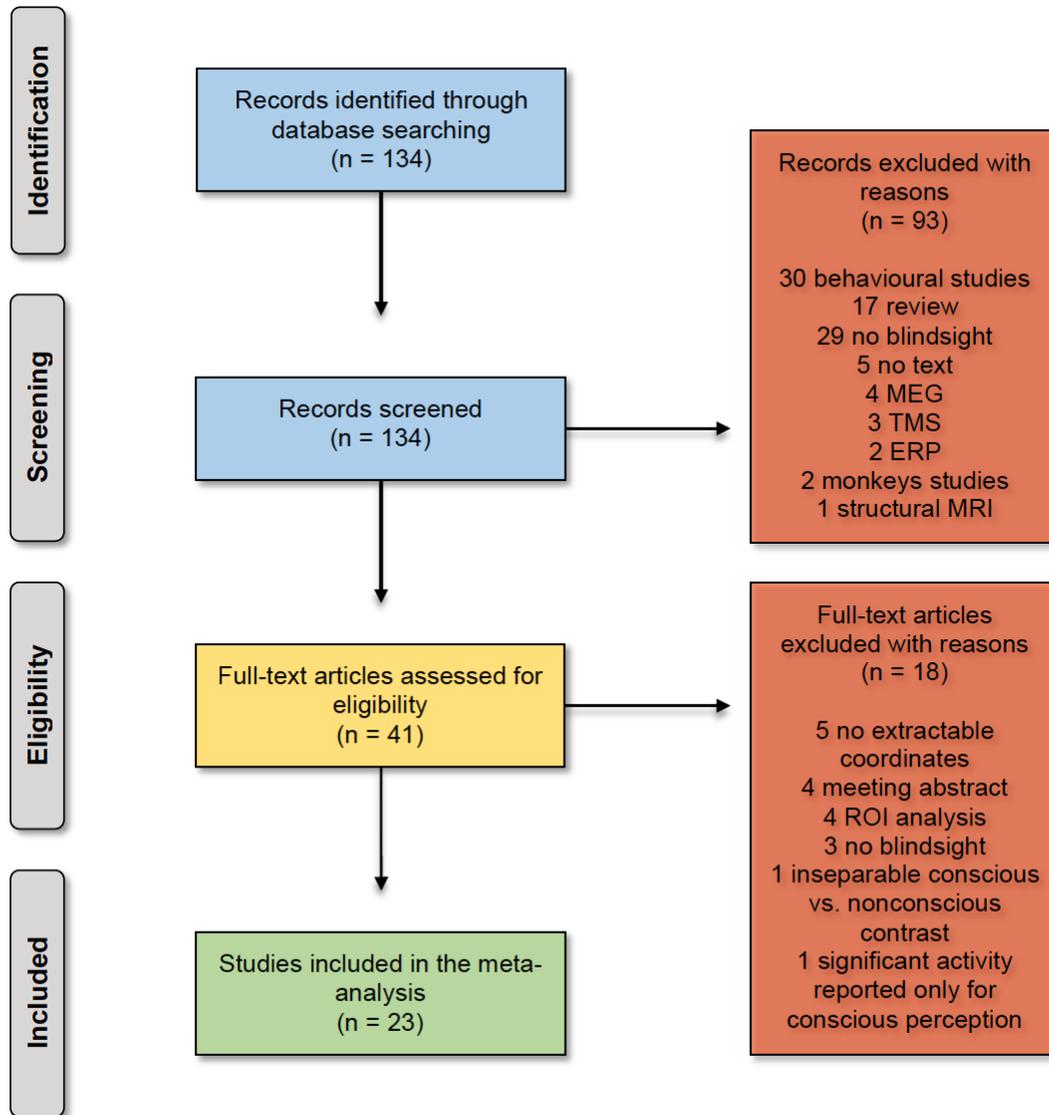
converted in a common space and then entered as input, thus avoiding arbitrary spatial assignments. Next, the foci are modelled as centres of Gaussian probability distributions and combined to create statistical whole-brain ALE maps (Eickhoff, Laird, Fox, Lancaster, & Fox, 2017). This means that the activations are weighted by the number of studies reporting it, as well as by the numerosity of the patients tested in each study, thereby accounting for the peculiarity of a literature essentially based on single-case studies. Finally, probability of activation and the derived metrics are calculated based on both individual voxel statistical significance and related to the original experimental details (Eickhoff, et al., 2016).

## **2. Methods**

### *2.1 Literature search and inclusion criteria*

A systematic search of the literature has identified relevant studies published before March 2017 and recorded in PubMed, Scopus and Google Scholar databases. During an initial phase, we entered the following keywords combined with an “OR” operator to identify peer-reviewed studies: “blindsight”, “residual vision”, “hemianopia”, “unconscious”, and “nonconscious”. These results were then combined using an “AND” operator with each of these additional search terms: “fMRI” “functional MRI” “PET” “neuroimaging”. Further relevant studies were pinpointed by searching through the reference lists of all previously identified papers. Twenty-three articles have been finally selected and included in the meta-analysis applying the following criteria: a) participants had to be adult human patients with blindsight (e.g. studies in monkeys or infants were excluded), b) only neuroimaging studies performed with fMRI or PET were retained, c) results needed to be based on whole-brain analyses (i.e. studies based only on region of interest – ROI – analyses were excluded), d) peak coordinates or parametric maps were reported in stereotaxic space (e.g., MNI or Talairach coordinates), or it was possible to derive the coordinates with accuracy, and, e) contrasts outlining

neural correlates of nonconscious processes were presented. The whole selection process and its outcomes are summarized in the PRISMA flow diagram displayed in Fig. 1 (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).



**Fig. 1.** PRISMA flow chart summarizing the selection procedure to identify the data-base of studies included in the meta-analysis.

Having finalized the selection procedure, we have then organized the relevant information from

each study in a database. Data concerning study sample, experimental settings including tasks demands and stimulus characteristics, and MRI methods were extracted. Twenty-three studies ultimately qualified and were retained for the meta-analysis, overall reporting 46 different experiments. Finally, the coordinates of significant peak activations from each experiment were reported in Talairach space. When necessary, the conversion from MNI to Talairach was done using the Lancaster transformation (Laird, et al., 2010) in the GingerALE software (version 2.3.6, <http://www.brainmap.org/ale/>). The selected studies along with the most relevant details in the experimental paradigms are reported in Table 1.

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Insert Table 1 about here

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## 2.2 Coordinate-based meta-analysis

Data were analysed according to standard ALE procedures (Laird, Fox, et al., 2005). The ALE is a voxel-based technique that models the spatial coherence of different fMRI results. A 3-dimensional Gaussian probability distribution is centred on each focus of every experimental contrast according to the following formula:

$$p(d) = \frac{1}{\sigma^3 \sqrt{(2\pi)^3}} e^{-\frac{d^2}{2\sigma^2}}$$

where  $d$  is the Euclidean distance between the voxels and the considered focus, and  $e$  is the spatial uncertainty. The standard deviation is calculated according to the method proposed by Eickhoff et al. (2009), which takes into account the number of subjects in each experiment computing the Full-Width Half-Maximum (FWHM) parameters as follows:

$$\sigma = \frac{FWHM}{\sqrt{8 \ln 2}}$$

The union of these Gaussian distributions gives rise to a modelled activation (MA) map for each experiment, and the final ALE map is generated by combining the individual MA maps. Corrections for multiple comparisons based on false-discovery rate (FDR) were applied at  $p < 0.05$ , in accordance with Eickhoff and colleagues (2012; 2017; 2016). The same threshold was also applied for cluster-level inference, which provides an unbiased assessment of the topological properties of the ALE maps with respect to the delineation of clusters formed by contiguously active voxels (Eickhoff, et al., 2017).

### 2.3. Quantification of the structure-function relationship, network similarities and clustering

We calculated the number of significant voxels in each source MA map and in every significant area, weighted by the overall number of voxels composing the same area. This resulted in a normalized matrix where the rows represent the neural areas, and the columns the source papers. From this matrix two vectorial representations of the data were generated: one in which the dimensionality of the space is defined by the number of active areas and each source article represents a point in this multi-dimensional space, and one in which, conversely, the dimensionality of the space is defined by the number of source articles.

The definition of these two spaces enabled us to quantify the relationships between each study and the activated brain areas in two complementary ways. First, we measured the percentage contribution of every single study to the identification of the neural structures collectively reported in the ALE map. Second, we assessed the inverse relationship; namely, how much each area composing the identified neural space is represented in the results of every study.

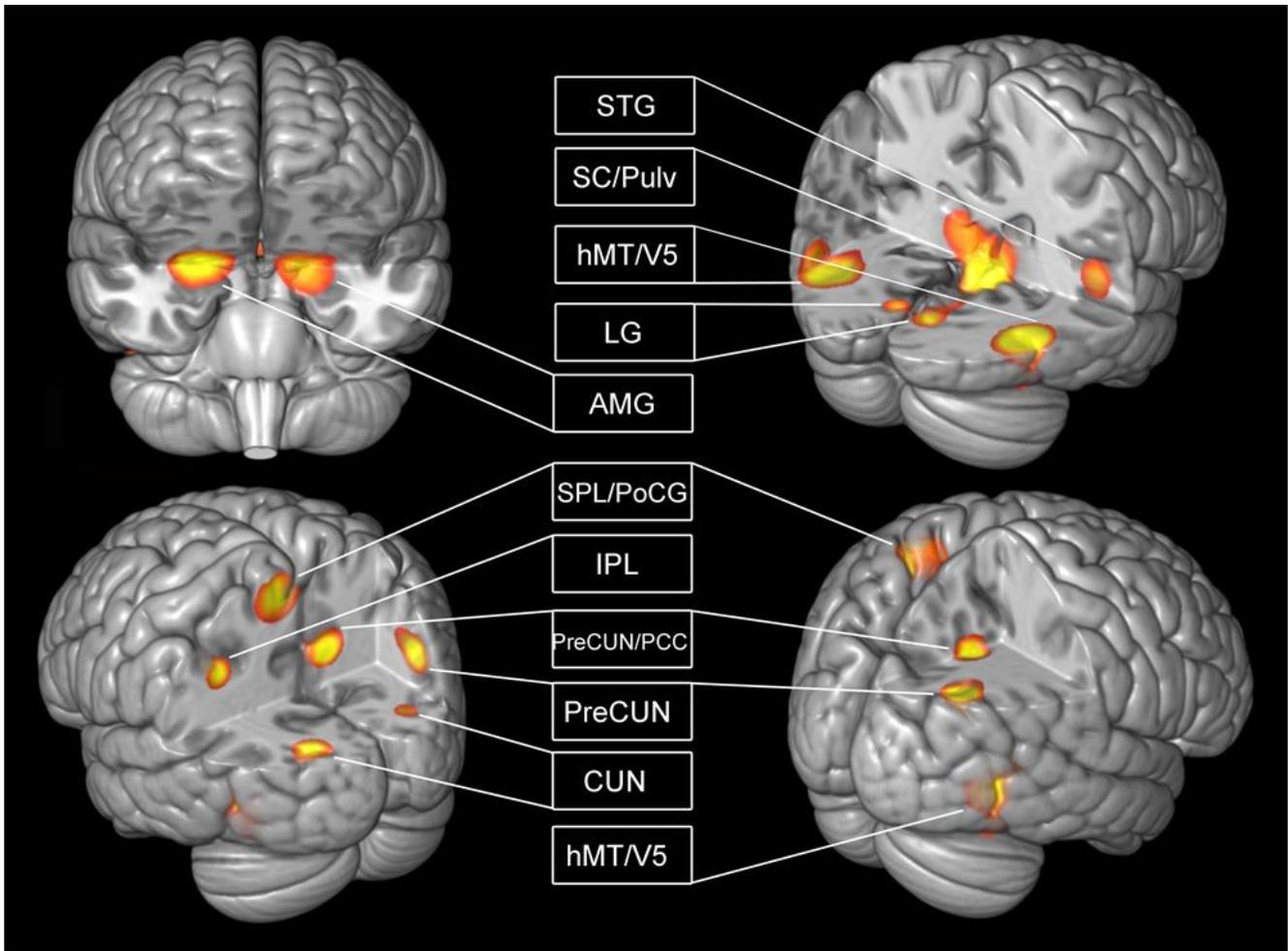
Lastly, the similarity between the activated areas and the reporting articles has been quantified and spatially represented by computing square distance matrices using Spearman metric, where higher values indicate closer similarities in a scale ranging from 0 to 1. The matrix was then reoriented to

minimize cross-correlation of diagonal values and submitted to a hierarchical clustering to obtain a dendrogram of networks based on average distance between entries. This procedure ultimately grouped data over a variety of scales by creating a cluster tree that represents the multi-level hierarchy, where clusters at root level are linked to clusters at the next level, and so on until the highest superordinate level is reached. Hierarchical clustering was applied to distance matrices of both neural areas and source articles by using the average linkage method, in which clusters are merged based on the average distance between the elements.

### **3. Results and Discussion**

#### *3.1. Neural fingerprint of blindsight*

The ALE meta-analysis found 14 significantly active brain regions, which collectively form part and parcel of the neurofunctional space of blindsight, as reported thus far in the available neuroimaging literature (Fig. 2 and Table 2). These regions include subcortical retino-recipient structures, such as the superior colliculus (SC) and the pulvinar (Pulv), the amygdala (AMG), and extrastriate areas along the dorsal as well as ventral visual stream, extending from the occipital to parietal and temporal cortices, respectively.



**Fig. 2.** Anatomical 3-D rendering of the ALE maps, collectively carving the functional neuroanatomy of blindsight ( $p < 0.05$  corrected for FDR).

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Insert Table 2 about here

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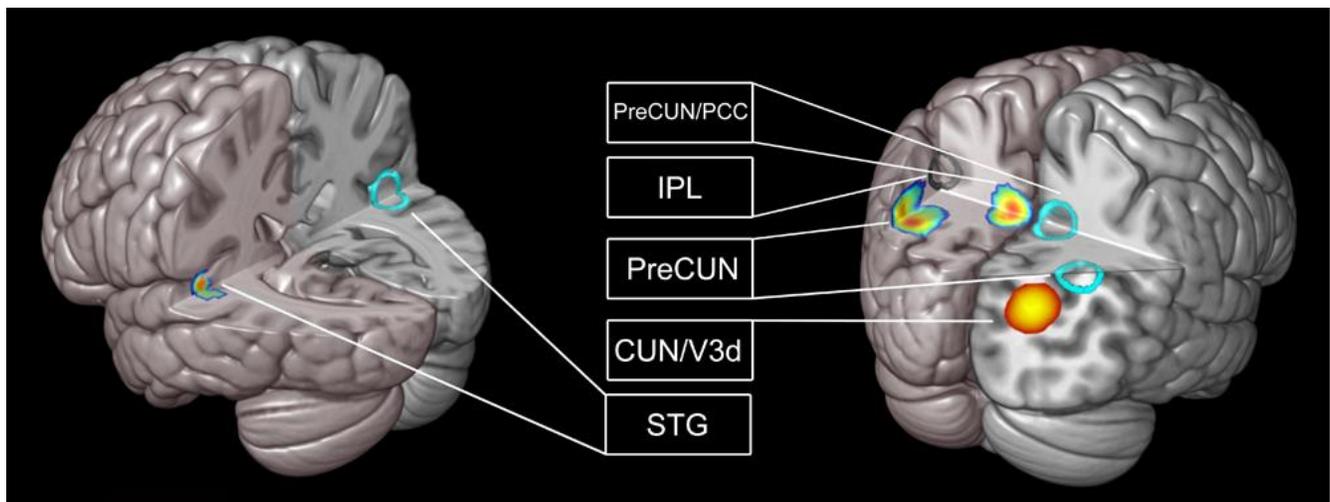
It is interesting to note the absence of significant activity in anterior frontal and prefrontal regions, whereas multiple foci could be found in higher-order posterior areas, including those located anteriorly in temporal cortex along areas compatible with sites considered the endpoint of ventral stream processing. This lends new support, admittedly indirect, to theories of conscious processing that assume a pivotal role for prefrontal activity causing top-down amplification, such as the higher-order

theories (Lau & Rosenthal, 2011), global workspace model (Dehaene & Changeux, 2011), or some forms of recurrent processing views (Lamme, 2006). Nevertheless, the present results should be interpreted with caution in the context of ongoing investigations on the neural correlates of consciousness. In fact, the nature of fMRI data is intrinsically correlational, and the same areas showing significant activity during nonconscious perception may have a response pattern fundamentally different from that observed in the intact brain, as in the case for instance of area hMT/V5 (Ajina, Kennard, Rees, & Bridge, 2015).

A longstanding issue that has come under renewed scrutiny concerns the possible contribution of the intact hemisphere to blindsight functions (Celeghin, Diano et al., 2017). It should be therefore informative to analyse the present data also in terms of activations in the ipsi-lesional vs. contra-lesional hemisphere. To this purpose, we performed a second ALE meta-analysis after re-organizing the database to align active areas to a uniform pathological template, as previously done by Ajina and colleagues (2014). Consequently, all patient-specific ipsi-lesional foci of activity were conventionally assigned to the “left” hemisphere, whereas all contra-lesional foci were assigned to the nominally “right” hemisphere. This required flipping the functional coordinates in the horizontal plane whenever necessary. Moreover, the study by Anders et al. (2004) was excluded from this second analysis because it was not possible to disentangle whether activity in the left parietal cortex was ipsi- or contra-lesional.

All significant activities originally localized in the left and right hemisphere using absolute coordinates were also found in the present analysis, with the following differences summarized in Figure 3. First, activity in the superior temporal gyrus (STG), lateral precuneus (preCUN) and mesial preCUN bordering the posterior cingulate cortex (PCC), which was originally detected in the right hemisphere, was indeed ipsi-lesional. Hence, these foci now appear flipped to the damaged (conventionally left) hemisphere. Second, activity in the right CUN results now significantly expanded.

The area encompasses a region bordering the infero-posterior part of the intra-parietal sulcus and the transverse occipital sulcus, approximately corresponding to cytoarchitectonic area hOC4d and to functionally defined area V3A (Abdollahi et al., 2014; Thiebaut de Schotten, Urbanski, Valabregue, Bayle & Volle, 2014). Third, activity in the left inferior parietal lobule (IPL) was no longer significant, due to the exclusion of the study by Anders et al., (2004) (see below for details).

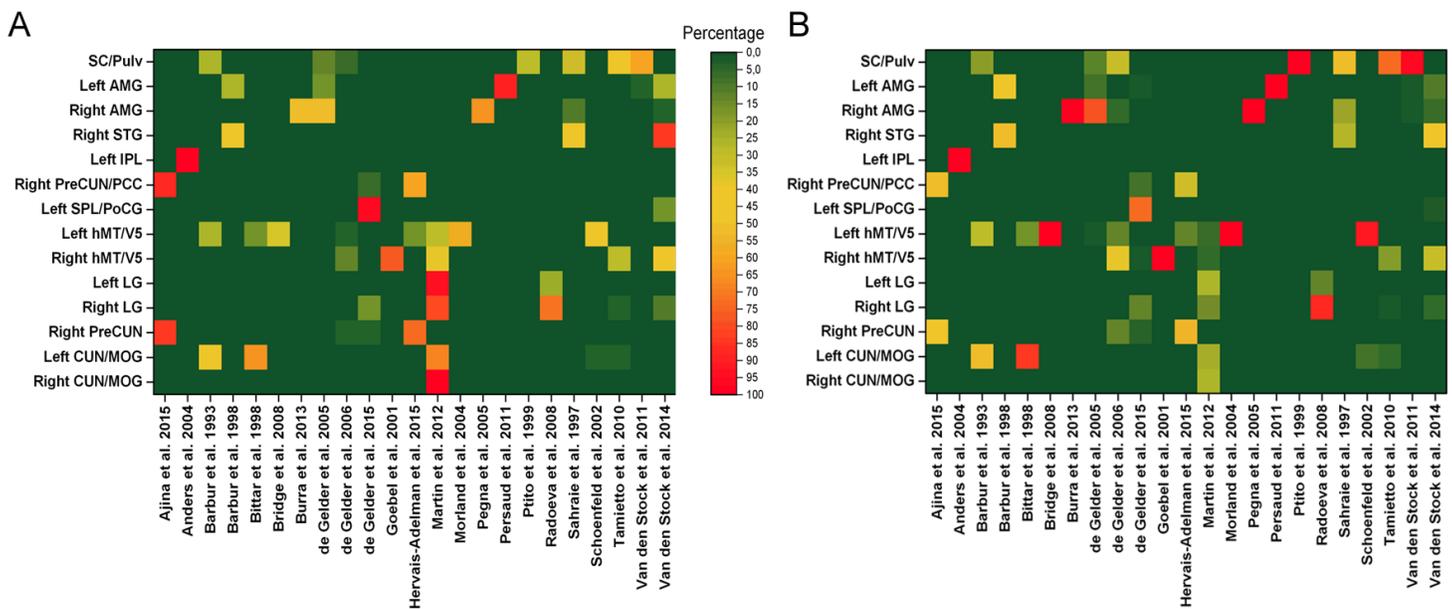


**Fig. 3.** Anatomical 3-D rendering of activities significantly different from those displayed in the previous ALE maps reported in Figure 2 ( $p < 0.05$  corrected for FDR). Ipsi-lesional activity is conventionally assigned to the left hemisphere (shaded in red), while contra-lesional activity is assigned to the right hemisphere. Foci in rainbow colour are those originally found in the right hemisphere and now conventionally flipped to the ipsi-lesional (left) hemisphere (empty cyan circles identify the previous location of the same foci). The newly reported active area in the contra-lesional (right) CUN is displayed in red-yellow colours. The empty grey circle in the ipsi-lesional IPL denotes that this area is no longer significantly active compared to the previous analysis.

### 3.2. Parcellation of the structure-function relationships

To better characterize the functional role of each structure, and link it with the different blindsight abilities defined by study-specific task demands and stimulus properties, we have investigated the reciprocal relationships between activated areas and individual studies. The normalized matrices, which are reported in Figure 4 as heatmaps, show an uneven and scattered distribution of the weights, thus indicating that the active structures were not equally involved in the different studies

tapping specific blindsight properties, and vice-versa. Predictably, the same structure appears in more than one study, according to contemporary models emphasising the notion that interacting and distributed brain networks underlie visual and cognitive functions (Anderson, Kinnison, & Pessoa, 2013; Bullmore & Sporns, 2012; Pessoa, 2014, 2017). Hence, it seems reasonable to search for network-level patterns in the anatomical architecture of blindsight as well; an aspect that will be addressed directly in the next section.



**Fig. 4.** Relationship between brain areas of significant activity and the original studies contributing their identification. (A) Data are normalized for areas, so that this heatmap is more informative when read from rows. (B) Data are normalized for contributing papers, and is more informative when read from columns.

Starting from subcortical structures, the SC and Pulv are mainly reported in studies presenting biologically salient stimuli, such as facial and bodily expressions, or moving stimuli, and in tasks often requiring direct forced-choice discrimination. Notably, the study contributing the most to the identification of this cluster is Van den Stock et al. (2011), which combined these two stimulus properties by presenting video clips of moving bodily expressions. Compatible with the role of these

structures in basic forms of visuo-motor integration and bottom-up attention (Celeghin, Barabas, et al., 2015), the second strongest contribution to their significant identification comes from a study assessing implicit bilateral summation; that is, the speeding up of reaction times for normally seen stimuli when they are paired with a task-irrelevant and unseen stimulus in the blind field (Tamietto, et al., 2010).

The AMG also appears prominently among subcortical activities, and its response seems mainly related to studies of affective blindsight, wherein emotional stimuli were presented. A notable exception is the study by Persaud et al. (2011), where a vertical square-wave grating was displayed in the blind field of patient G.Y., who was asked to “guess” its location by choosing between upper and lower visual quadrants. Notably, however, a variant of the post-decision wagering task was introduced in this study, and the patient could gain or lose 50 pence for each response. As the authors acknowledged, this might have introduced in the setting an emotional component with associated feelings that can likely explain AMG activation. Lastly, there is a noteworthy trend toward lateralized activity in the right AMG. A preferential involvement of the right AMG during nonconscious emotion processing was originally proposed in neuroimaging studies applying backward masking to healthy participants, and seems corroborated by the present results (Morris, Ohman, & Dolan, 1998).

At the cortical level, a strong and straightforward relationship concerns the fairly bilateral activation of motion sensitive area hMT/V5 in virtually all studies that presented moving stimuli, either from dots, wedges, or biological motion, and that compared coherent vs. incoherent movements. Interestingly, a few studies reporting hMT/V5 presented static images of bodily expressions that, according to the interpretation originally proposed, imply movement processing and elicit spontaneous attribution of the actually missing motion information (de Gelder & Hadjikhani, 2006; Van den Stock, et al., 2014). Along the ventral stream, the most significant activity was found in a rather anterior cluster along the STG. Activity in this area was primarily driven by studies presenting complex forms

like faces, bodies and objects (Van den Stock, et al., 2014), or requiring colour discrimination (Barbur, Sahraie, Simmons, Weiskrantz, & Williams, 1998). The role of ventral stream areas in complex form and shape discrimination, as well as in colour perception, is well-established (Kravitz, Saleem, Baker, Ungerleider, & Mishkin, 2013). More tellingly, classic neuropsychological investigations report selective impairments of form or colour perception, such as visual agnosia (De Renzi, Faglioni, Grossi, & Nichelli, 1991) or achromatopsia (Cole, Heywood, Kentridge, Fairholm, & Cowey, 2003; Kentridge, Heywood, & Cowey, 2004), respectively, in patients with focal lesions affecting temporal lobes.

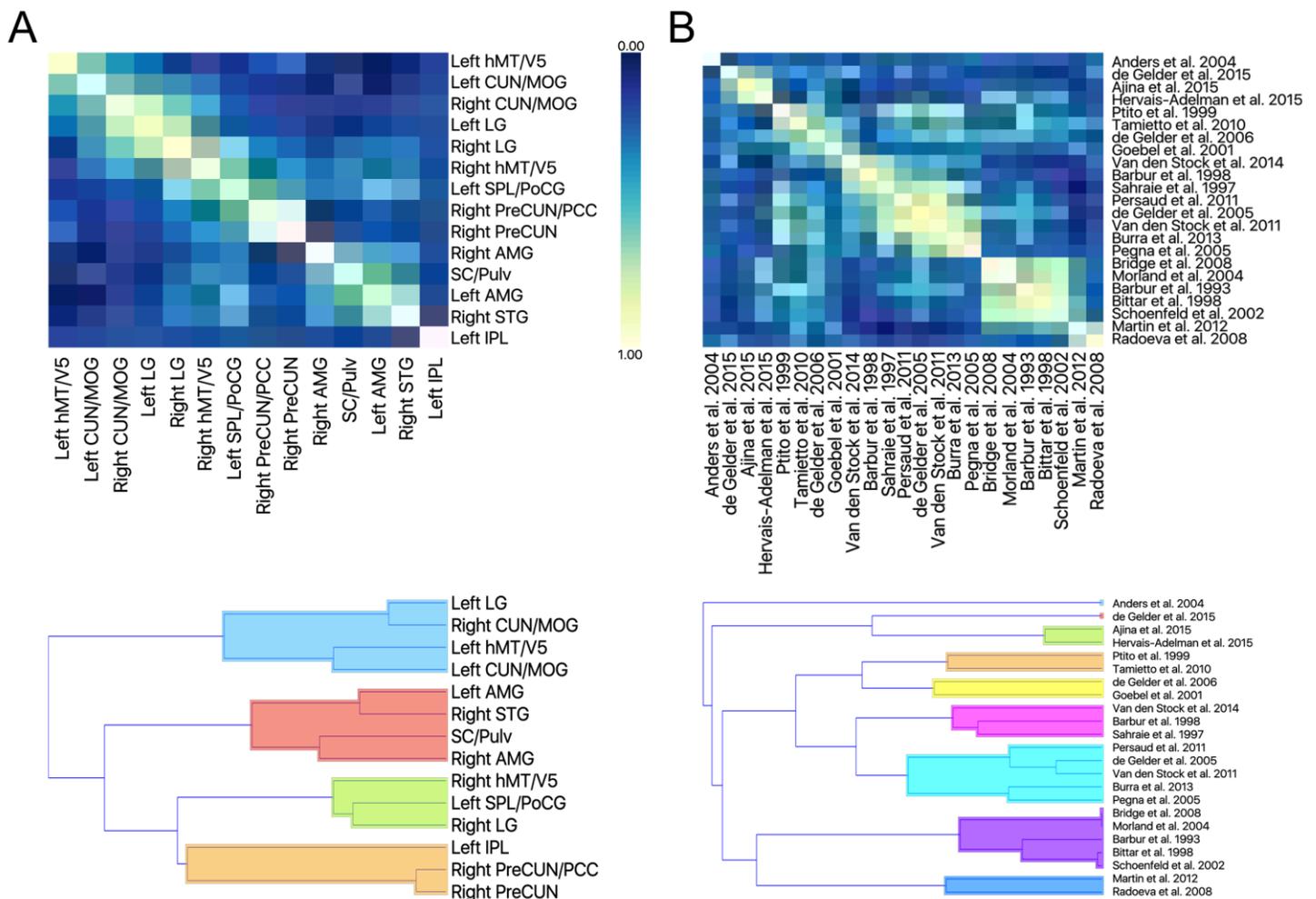
Dorsal stream activity in lateral and mesial portions of the preCUN was reported in response to coherent motion and for looming stimuli (Ajina, Kennard, Rees, & Bridge, 2015; Hervais-Adelman, et al., 2015). This is compatible with the attentional role of these areas in relation, for example, to visuo-motor integration, as when collision needs to be avoided and global motion direction has to be extracted from multiple moving dots. Another dorsal focus was detected in the left IPL and determined by the significant activity reported by Anders et al. (2004). In this study, blindsight patients were asked to perform an internal monitoring task, and to report subjective feelings associated with the presentation of unseen faces paired with aversive screams. Activity in IPL was linked to the level of correspondence between reported experience and measured psychophysiological responses. Therefore, IPL activity appears in relation with attentional mechanisms in the context of interoceptive monitoring (Tamietto, et al., 2015).

Lastly, activity in early peri-striate of extrastriate areas in the lingual gyrus (LG) and CUN was found in studies presenting moving stimuli and requiring direct discrimination (Barbur, et al., 1998; Bittar, Ptito, Faubert, Dumoulin, & Ptito, 1999; Martin, Das, & Huxlin, 2012; Radoeva, Prasad, Brainard, & Aguirre, 2008). From the present data, it is difficult to tell whether these early areas serve the rather unspecific function of relaying visual information to higher order areas with finer-tuned

selectivity for specific stimulus attributes, or bear more intrinsic response specificity to either stimulus properties or task demands (Tamietto & Leopold, 2018). However, more clues can be derived from the clustering analysis that reports which structures coalesce more and hierarchical arrangement of their co-activations.

### 3.2. Network similarities and hierarchical clustering

Similarity matrices reveal a non-random aggregation of the activated areas and of the source articles, with higher values indicating closer similarity between items. This resulted in hierarchical clustering of structures and articles at multiple levels (Fig. 5).



**Fig. 5.** Distance matrix and hierarchical clustering between brain areas and between contributing studies included in the meta-analysis. (A) Upper panel displays the square distance matrix among active brain areas, where higher values indicate closer similarities. Lower panel reports a dendrogram of brain networks resulting from hierarchical clustering of the distance matrix among active areas. (B) The same information as in panel A is reported, but based on contributing articles rather than on brain areas.

As far as the organization of active areas is concerned, their response co-occurrence led to the formation of four distinct hierarchical clusters. A first cluster included early extra-striate structures such as the LG and CUN/MOG together with hMT/V5, prevailing in the left hemisphere. The functional meaning of this cluster thus seems concerned with nonconscious movement perception. The aggregation of this set of areas when blindsight studies are meta-analytically pooled together is in keeping with the known functional and connectional properties of area hMT/V5 (Born & Bradley, 2005). As it happens, hMT/V5 receives direct subcortical input from LGN (Sincich, Park, Wohlgenuth, & Horton, 2004) as well as from the pulvinar (Bridge, Leopold, & Bourne, 2015), thereby bypassing V1, and these connections seem critical for nonconscious movement perception (Ajina, Pestilli, Rokem, Kennard, & Bridge, 2015). Moreover, hMT/V5 receives cortical input directly from V2 and V3, besides sequential feedforward of visual information along cortical hierarchy. As a consequence, its response characteristics (Ajina, Kennard, et al., 2015) as well as connectional architecture (Warner, et al., 2015) undergo substantial reorganization following V1 damage, possibly because hMT/V5 reshapes its activity and network properties on the basis of remaining input from spared subcortical and extrastriate areas (Tinelli, et al., 2013).

The second cluster comprises subcortical structures, such as SC, Pulv and AMG, and the STG. Its functional role is presumably related to nonconscious emotion processing, as this network has been extensively reported in studies of affective blindsight (Celeghin, de Gelder, et al., 2015; Diano, Celeghin, Bagnis, & Tamietto, 2017). The existence of a subcortical pathway to the amygdala devoted to nonconscious emotion perception, as originally envisaged by LeDoux's works (LeDoux, 1996), has

been demonstrated in patients with blindsight as well as in healthy participants, and across a variety of methods, including fMRI, MEG, tractography and cell recordings in both humans and monkeys (Garrido, Barnes, Sahani, & Dolan, 2012; Liddell, et al., 2005; Méndez-Bértolo, et al., 2016; Rafal, et al., 2015; Tamietto, Pullens, de Gelder, Weiskrantz, & Goebel, 2012). Equally plausible is the co-activation of the temporal cortex, given the abundant and reciprocal connections of this area with the AMG (Whalen & Phelps, 2009) and their psychophysiological interactions (Diano, Tamietto, et al., 2017).

The third cluster, containing right hMT/V5, LG, and left SPL, seems to reflect functional principles of organization similar to those discussed for the first cluster, which also included hMT/V5 and LG, but in the left hemisphere. Whether this lateralization reflects meaningful organizational properties in networks for nonconscious movement perception, remains to be established and lags behind the statistical power achievable with the present sample. However, a proper evaluation of this issue in blindsight, as in any other group of patients with unilateral lesions, requires the intersection of two different laterality principles: the hemispheric side of the lesion, and that of the reported activity. Along this line, we offer several tentative interpretations of the present data. Compared to the first cluster with similar areas in the opposite hemisphere, data contributing activations in the present cluster were chiefly derived from patient G.Y., the study by Martin et al (2012) being the only exception. Since patient G.Y. suffered damage to his left V1, the present cluster could outline the functional contribution of the contralesional (intact) hemisphere in response to ipsilateral stimulation of the blind right visual field. Adaptive compensation of motor or cognitive functions following unilateral damage to frontal or parietal cortex has been extensively documented (Johansen-Berg, et al., 2002; Passingham, 1993), and a similar mechanism for nonconscious visual functions after occipital lesion has been recently demonstrated (Celeghin, Diano et al., 2017; Celeghin, Barabas, et al., 2015; Georgy, Celeghin, Marzi, Tamietto, & Ptito, 2016). Hence, the present findings plead for thorough examination of this

aspect in future studies. Finally, the bulk of papers reporting these structures in their results have heavily relied on active tasks and direct forced-choice methods. It is thus conceivable that the present aggregation partly reflects functional areas more involved in explicit decision-making about the nature of unseen stimuli.

The fourth, and last, cluster included different sites in the preCUN and in IPL. The dorsal location of these foci suggests a relationship with the endogenous vs. exogenous shift of attentional focus (Kentridge, Heywood, & Weiskrantz, 2004), and with visuo-motor functions (Milner & Goodale, 2006), rather than with clearly defined stimulus properties. In fact, the primary determinant of significant activity in IPL was the study by Anders et al. (2004), where emotional feelings and interoceptive changes had to be reported. On the other hand, preCUN sites were mainly contributed by studies presenting looming stimuli and motion coherence (Ajina, Kennard, et al., 2015; Hervais-Adelman, et al., 2015), which are also known to summon attention and trigger sensory-motor integration.

The reciprocal distances between studies and their hierarchical organization partly reproduce considerations and organization principles already discussed in the clustering of neural structures, with proximities between studies performed by the same laboratories more readily appreciable (Fig. 5B). Additionally, it is worth mentioning that the finer-grained clustering on this dataset partly reflects the relative disaggregation of two studies: Anders et al. (2004) and de Gelder et al. (2015). These studies are indeed quite unusual for their task demands, compared to other experiments on blindsight, as they asked patients to perform self-report of emotional feelings and mental imagery, respectively. Therefore, while the aggregation pattern of neural structures seems to hold meaning primarily when interpreted from the perspective of stimulus properties, analysing data from the point of view of single studies possibly brings more into focus peculiarities in task requirements.

#### **4. Conclusions**

After more than four decades from its original discovery, blindsight has been challenged by a number of healthy criticisms, either related to experimental details in the methodologies used to test it, or to the anatomical and functional completeness of V1 destruction (Campion, Latto, & Smith, 1983; Cowey, 2010; Wessinger, Fendrich, & Gazzaniga, 1997). Over the years, across different laboratories, and in different patients, these criticisms have been carefully addressed and almost invariably dismissed. As a result, even the most sceptical investigator cannot demote the phenomenon to an artefact.

What remains contentious, however, is the elusive nature of blindsight's functional neuroanatomy. We suggest that the conceptualization of blindsight as a constellation of multiple nonconscious visual abilities is better apt as a summary of present-day wisdom, rather than its view as a monolithically unitary phenomenon (Tamietto & Morrone, 2016). This, in turn, reflects the variety of existing V1-independent pathway and their role in sustaining different spared functions. In this context, the present study has offered the first data-driven charting of the functional neuroanatomy of blindsight, as emerging from the current body of neuroimaging literature. In doing so, we have exploited meta-analytic methods and bent their computational properties to account for the peculiarities in the nature of the data. This, we hope, can add methodological value, and can contribute to establish a better meta-analytical framework more sensitive to the specificities in the studies examined.

A few concluding considerations are in order. The relationship between active areas and experimental details in the contributing papers suggests that the intersection between stimulus properties and task requirements is fruitful to devise more comprehensive taxonomies. With respect to stimulus properties, a broad tripartite distinction among moving stimuli, processing of shape, colour or complex forms, and perception of emotionally or biologically salient stimuli, such as faces and bodies, seems to capture this dimension. As far as task requirements are concerned, the classification proposed by Danckert and Rossetti (2005) appears relatively compatible with the present results. The original

categorization was indeed mainly based on the “*behaviours demonstrated by blindsight patients*”, and distinguished “*action blindsight*”, “*attention blindsight*”, and perceptual judgments. This classification, as well as others, is inevitably incomplete and intrinsically provisional. Hence, continuous updating is required as long as research proceeds and new findings come to light. Just to make one example, the discovery of affective blindsight figures prominently as a newcomer, and was not reported in previous categorizations. Nevertheless, we tend to think that taxonomies of this kind hold heuristic value in systems neuroscience and neuropsychology, and can be helpful to foster blindsight research toward underexplored directions.

Several important studies were excluded from the present analysis for the reasons summarized in Figure 1. This is not meant to detract value from these studies, but simply reflects our methodological choice to provide a picture as data-driven and anatomically precise as possible. For example, data from ROI analyses were excluded. This was decided because the application of an ROI introduces a-priori constraints with respect to whole-brain analysis, and limits from the outset the number of active structures that can be found. Similarly, papers not reporting activation coordinates, or not displaying a clear figure in native space from which the anatomical location of activated structures could be reasonably derived, were not considered. This has helped in reducing spatial uncertainty, but also bears a trade-off concerning statistical power. Moreover, pooling together group and single-case studies, even given the weighting incorporated into the model, can lead to underestimation of brain areas contributed by group studies. This happens because the mixed-effects analysis, which is normally performed in group-studies to take into account inter-subject variance, may lead to responses weaker than the corresponding activities in single-cases. Lastly, the spatial resolution achievable cannot disentangle activations in close proximities, especially at the subcortical level. Regrettably, the present data cannot thus contribute to the thriving investigation on the role of signal relay from LGN and pulvinar in driving hMT/V5 activity when V1 input is abolished (Ajina, Pestilli, et al., 2015; Bridge, et

al., 2015).

In summary, the present meta-analytical study enabled us link information processing in blindsight with the network-based and hierarchical organization of its functional neuroanatomy, which seemingly reflects the different stimulus properties and the variety of task demands that have thus far characterized the empirical investigation of this fascinating phenomenon.

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**TABLES**

**Table 1**

Overview of the 23 studies included in the meta-analysis.

<b>First author</b>	<b>Year</b>	<b>N. Subjects</b>	<b>Age</b>	<b>Task</b>	<b>Stimuli and Contrasts</b>
Ajina	2015	7	38-76	Passive viewing	Coherent vs. incoherent moving dots
Anders	2004	8	NA	Self-reported emotional feelings	Neutral faces paired with aversive scream
Barbur	1993	1	36	Motion discrimination	Moving vs. stationary bars
Barbur	1998	1	41	Colour discrimination	Red or green vs. achromatic checkerboards
Bittar	1999	1	25	Passive viewing	Vertically moving gratings vs. randomly moving dots
Bridge	2008	1	53	Passive viewing	Moving vs. stationary dots
Burra	2013	1	57	Passive viewing	Neutral faces with direct vs. averted gaze
de Gelder	2005	1	45	Expression discrimination of seen images during redundant target	(In)congruence between seen and unseen fearful, happy and IAPS stimuli
de Gelder	2006	1	46	Expression discrimination	Happy vs. neutral bodily expressions
de Gelder	2015	1	59	Mental imagery	Mental imagery of angry persons vs. tree during exposure to neutral or affective images
Goebel	2001	2	54.5	Stimulus detection	Rotating vs. static spirals, coloured objects vs. baseline
Hervais-Adelman	2015	1	62	Passive viewing	Looming vs. receding, rotating or stationary point lights
Martin	2012	4	61	Motion discrimination	Globally coherent vs. random moving dots
Morland	2004	2	54.5	Motion discrimination	Moving vs. stationary gratings
Pegna	2005	1	52	Emotion discrimination (outside scanner)	Emotional vs. neutral facial expression
Persaud	2011	1	52	Location discrimination	Location discrimination
Ptito	1999	1	31	Passive viewing	Moving gratings vs. random dot background
Radoeva	2008	1	21	Motion detection	Checkerboard stimulus

Sahraie	1997	1	41	Motion discrimination and aware/unaware classification	Direction discrimination of moving dots
Schoenfeld	2002	1	22	Movement and colour change detection (outside scanner)	Moving and colour changing bars vs. baseline fixation
Tamietto	2010	1	52	Detection of seen stimuli during redundant target	Bilateral vs. unilateral grey or purple squares
Van den Stock	2011	1	53	Emotion discrimination	Angry vs. neutral whole-body dynamic moving actions
Van den Stock	2014	1	59	Category discrimination (outside scanner)	Neutral faces or bodies vs. objects or scrambled images

*Abbreviations:* IAPS= International Affective Picture System.

**Table 2**

Brain areas significantly active in the ALE meta-analysis ( $p < 0.05$ , FDR) and cluster size (1 voxel = 8 mm<sup>3</sup>). Local maxima are reported in Talairach coordinates.

Lobe	Surface	Brain Areas	Hemisphere	N. Voxels	Z	Talairach coordinates		
						X	Y	Z
<i>Sub-cortical</i>								
		SC/Pulv		1629	3.38	-2	-30	0
	<i>Limbic</i>							
		AMG	L	731	3.01	-18	-4	-12
		AMG	R	1202	3.77	20	-4	-10
	<i>Temporal</i>							
	<i>Lateral</i>							
		STG	R	249	2.87	52	-30	12
		hMT/V5	L	1571	3.80	-42	-68	-4
		hMT/V5	R	1381	5.21	44	-64	0
	<i>Parietal</i>							
	<i>Lateral</i>							
		IPL	L	212	3.90	-42	-44	42
		SPL/PoCG	L	664	3.58	-14	-52	66
	<i>Mesial</i>							
		preCUN	R	385	3.72	34	-70	36
		preCUN/PCC	R	263	4.16	10	-48	34
	<i>Occipital</i>							
	<i>Mesial</i>							
		LG	L	83	3.04	-8	-74	-4
		LG	R	273	2.58	8	-70	0
	<i>Lateral</i>							
		CUN/MOG	L	239	3.49	-24	-84	18
		CUN/MOG	R	57	2.89	20	-82	18

*Abbreviations:* AMG = amygdala; CUN = cuneus; SC/Pulv = superior colliculus/pulvinar; hMT/V5 = human motion areas; IPL = inferior parietal lobule; LG = lingual gyrus; MOG = middle occipital gyrus; PCC = posterior cingulate cortex; preCUN = precuneus; SPL/PoCG = superior parietal lobule/post-central gyrus; STG = superior temporal gyrus.

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