Title: A Way to The Light: Pathways Mediating Blindsight After V1 Injury: A Systematic Review of Human and Monkey Studies

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Abstract

Objective: Despite injury to area V1 resulting in visual impairment, some patients maintain visual capabilities in an unconscious manner, a phenomenon called blindsight. This systematic review critically evaluates the role of neural pathways that facilitate blindsight.

Methods: The review comprehensively assesses research from online databases. Following the screening process, we employed the JBI critical appraisal checklist and the SYRCLE tool for the assessment of risks in human and animal studies. Two authors conducted separate evaluations of each study. Every disagreement was effectively settled by mutual agreement. We selected 25 articles focusing on the mediating pathways of blindsight.

Results: In humans, the pathways from the Lateral Geniculate Nucleus (LGN) to V5, from the Superior Colliculus (SC) to higher brain areas, and to the remaining segments of V1 are crucial. The pathway that connects the SC, pulvinar, and amygdala is essential for processing emotional visual information. Studies conducted on animals emphasize how important the SC-Pulvinar pathway and the connections between the LGN and extrastriate areas are for developing blindsight.

Conclusion: Individual differences in neuroplasticity, the precise site and timing of the damage, and the amount of time that has passed since the injury all play a major role in the activation of pathways that enable blindsight. This demonstrates a complicated system that successfully lessens the loss of the primary visual cortex, highlighting the necessity of developing rehabilitation plans that are specific to each individual with visual impairments.

Keywords: Blindsight, Residual vision, Lateral Geniculate Nucleus, Superior Colliculus, V1 islands

Introduction

After the sensation by specific receptors in the eye, the visual data travels through the pathway to the Lateral Geniculate Nucleus (LGN) in the thalamus, then through area V1 to higher cortical regions. This main path is called the Reticulogeniculostriate pathway. Damage to area V1 interrupts this pathway, causing loss of "conscious vision" (Celesia, 2010). However, extensive research has shown that some patients retain the ability to respond to stimuli within their scotoma-localized area of diminished vision, even if not consciously, which is called blindsight (Weiskrantz et al., 1974). For example, studies showed a wide range of residual functions, including shape discrimination, object recognition (Trevethan et al., 2007; Van den Stock et al., 2015; Van den Stock et al., 2014; Weiskrantz, 1987), color perception (Kentridge et al., 2007; Morland et al., 1999), recognition of emotions (Bertini et al., 2013; Gerbella et al., 2019; Pegna et al., 2005; Van den Stock et al., 2011), manual localization, actions towards or spontaneous anti-pointing of unseen targets (de Gelder et al., 2008; Smits et al., 2019), processing gaze direction (Burra et al., 2013), and movement detection (Grasso et al., 2020; Hervais-Adelman et al., 2015) in case of applying pressure by the examiner. In this context, the ability to perceive emotions unconsciously is called affective blindsight, while other types are termed non-affective. The question here is which path or pathways in the brain can be attributed to blindsight. Various hypotheses and ideas have been proposed to explain blindsight.

A group of studies believe that area V1 is not obliterated after damage, and the small remaining islands continue to function. These islands are not large enough to make conscious vision but enough to allow a person to respond to a stimulus unconsciously (Kalat, 2015; Radoeva et al., 2008). For example, through functional MRI (fMRI) studies of a patient, it was found that the patient can unconsciously perceive movements through the tiny islands left in his V1 area (Morland et al., 2004). Some researchers also claimed the role of the remaining islands of V1 in blindsight (Papanikolaou et al., 2019). Contrary to this hypothesis, some people still have unconscious vision despite completely losing the V1 area (Morland et al., 2004;

Papanikolaou et al., 2019; Radoeva et al., 2008; Tran et al., 2019) questioning the sufficiency of V1 islands in mediating blindsight.

The second group claims that the LGN is central to this phenomenon. Two pathways extend from LGN to higher brain areas: one transmits information to V1, or striate cortex (the striate cortical area responsible for processing visual information), and the other bypasses V1, sending information directly to the extrastriate cortex. These articles highlight the role of LGN-Extrastriate pathways in the emergence of blindsight (Schmid et al., 2010). The study (Ajina & Bridge, 2019) on a person with bilateral V1 damage shows that LGN to Middle Temporal (MT) region pathways facilitate motion detection. (Bridge et al., 2010) demonstrated that in bilateral V1 damage, direct pathways from LGN to MT enable unconscious movement detection.

The last group of researchers considers the role of the Superior Colliculus (SC) in the emergence of blindsight. They believe that pathways passing through this area, which transfer information directly from the eye to regions above V1, play a prominent role. After surgical removal of the V1 area in two monkeys, (Kato et al., 2011) demonstrated the role of retinotectal pathways through SC in blindsight. However, another study using artificial induction of blindsight by Transcranial Magnetic Stimulation (TMS) rejected this role (Allen et al., 2014).

The phenomenon of blindsight has been extensively examined by neuroscientists for decades, resulting in a substantial body of literature. Each article has analyzed the topic from diverse perspectives, utilizing distinct methodologies. Considering methodological, chronological, and technical disparities, essential components must be identified and conclusions formulated accordingly. Thus, conducting a systematic review in this domain becomes necessary to direct future research toward these pathways to enhance understanding and develop rehabilitation treatments for people experiencing V1 injury.

Materials and methods

A systematic review of published studies until 10 August 2024 was conducted. No language limit has been considered. Inclusion criteria required studies to be original research articles that demonstrated precise methodology and robust evidence of pathway activation in blindsight. Due to the anatomical and functional similarities in their visual systems, only studies on humans and monkeys were included to provide a comprehensive understanding of blindsight pathways. Research on monkeys allows for more controlled experimental conditions, which can observe the effects of V1 damage in ways that are not ethically or practically feasible in human studies. This strengthens our understanding of how these pathways operate across species, ultimately supporting the translational potential of these findings in clinical settings.

Exclusion criteria involved studies in which the damage to the V1 region was ambiguous, and the proposed pathways of blindsight were not mentioned or, if mentioned, did not provide significant evidence. We excluded cases of hemispherectomy due to the inability to examine the interaction between both hemispheres and accurately trace compensatory pathways in this phenomenon. These criteria aimed to ensure repeatability and clarity in data selection, enhancing the rigor of this systematic review.

Search in database, screening, and data extraction

We searched online databases such as Pubmed, SCOPUS, Web of Sciences, and Embase, extracting all related articles. Search syntaxes are provided in supplements.

In the first step, articles were assessed based on title, and the articles with irrelevant titles were excluded. In the second step, the abstracts of the chosen articles were reviewed. Then, full texts of approved articles were reviewed, selecting studies on humans or monkeys that mentioned pathways facilitating blindsight. After reading the full texts, we used the JBI Critical Appraisal Checklist for human studies and the SYRCLE tool for animal studies for risk assessment. Two authors independently evaluated studies, resolving

disagreements through discussion and consensus. The primary search retrieved ۷۶۱۶ articles from the databases, 1429 of which were identified as duplicates. After reviewing the titles and abstracts, 836 articles were selected for full-text analysis. Based on the inclusion criteria, 25 articles were selected for data extraction. Figure 1 displays the process of choosing the eligible articles.

The reported data include publication year and country, first author's name, study type, age, sex and number of cases/controls, V1 injury mechanism, injury onset age, time elapsed since injury, injury location, type of task, and stimuli used to assess blindsight existence and its responsible pathways, imaging tool, and proposed pathways mediating blindsight. Two reviewers independently extracted data using pre-structured data sheets. The data are presented in Tables 1-6.

Quality assessment

The JBI Critical Appraisal Checklist was used to assess the quality of the human studies, and the SYRCLE risk assessment tool was used for animal studies. Two authors independently evaluated each study. All differences of opinion were settled by discussion and mutual agreement. The case-control studies (n=9) were assessed based on 10 criteria for study design, participant selection, exposure and outcome measurement, and statistical analysis. Studies that showed a high risk of bias in two or more domains were considered to have an overall high risk of bias. Overall, the quality assessment revealed that most case-control studies had a low or unclear risk of bias, indicating good study design and conduct. While the quality of reporting in the case-control studies was generally good, some studies did not adequately consider confounding factors or grouping techniques. 10 case reports and the only case series were evaluated on eight criteria for clear, detailed patient descriptions and presentations. Most of the studies were assessed as low-risk and did not have significant issues. Animal studies (n=5) were evaluated by the SYRCLE risk

assessment tool based on 10 criteria related to study design, grouping, exposure, and outcome measurement. Overall, the quality assessment of experimental studies revealed that most had a moderate risk of bias.

Results

We assessed 25 articles, including 20 human studies and five monkey studies. Five of the 20 human articles focused on affective blindsight and 15 on non-affective blindsight. Among all human studies, 10 were case reports, nine were case-control studies, and one was a case series (Table 1). The mechanisms by which the area V1 was injured or inactivated are as follows: 46 patients had V1 injury due to Cerebrovascular Accidents (CVA), six cases had trauma, four cases had undergone surgery, one case had an Arteriovenous Malformation (AVM), one case experienced ischemia due to asphyxia, one case had tumor, and five patients had lesions due to hypoxia of unknown origin. Additionally, there were 16 cases of TMS-induced V1 inactivation (Table 2). To categorize the tasks through which the cases were asked to detect the stimuli, the articles were divided into the following categories: seven articles used passive viewing, three used emotion discrimination, five used direction discrimination, five used stimuli (onset) detection, and two used color discrimination as tasks to examine the blindsight-mediating pathways. Regarding the imaging tools used, 14 articles chose fMRI to identify pathways; two used Electroencephalography (EEG) and Visual Evoked Potential (VEP), one used PET scan, and two used Diffusion-Weighted MRI (DW-MRI) (Table 3). There were also five monkey studies, with eight monkeys participating (Table 4). The injury mechanism in the cases of four of these studies was the surgical removal of the V1 area by aspiration. The injury was unilateral in all cases. One article did not mention the number of its cases and their injury mechanisms (Table 5). The task involved stimulation detection through visually guided saccades. Each study used the inactivation of different brain parts to assess the effects on behavior; one study also employed fMRI for pathway assessment (Table 6).

Main findings

Human studies

Four articles supported that the SC-Pulvinar-Amygdala pathway facilitates emotion detection in affective blindsight. Among those, three studies used emotion discrimination, and one used a passive viewing task. (Pegna et al., 2005) showed that facial expressions, especially fear, are processed via this route, as evidenced by increased right amygdala activation. Higher cortical areas' role was also emphasized in more complex emotional processing before reaching the amygdala. However, another study involving one patient who performed a passive viewing task and was evaluated by EEG presented different results. The results of this study question the existence of a direct SC-Pulvinar-Amygdala route. Similar to the former research regarding more complex emotions, this study implicates an indirect pathway that transits from the extrastriate cortex through anterior areas and finally ends in the amygdala (Andino et al., 2009).

In cases of non-affective blindsight, three studies supported the idea that blindsight occurs due to the function of spared islands of V1. However, all these studies also found V1 bypassing pathways that sometimes reach MT. The tasks performed by patients were as follows: one direction discrimination, one color change detection, one stimulus and direction detection along with shape and color discrimination, plus detection of moving stimuli of variable contrast levels. All these studies used fMRI to determine the pathway.

Six articles supported the pathway from LGN to MT (both in the injured hemisphere), with 55 cases. The tasks were as follows: two studies used stimulus and direction detection, one study used both passive viewing and movement detection, one study used stimulus and motion detection along with color discrimination and localization tasks, and two used passive viewing. The tools used were as follows: three studies used fMRI, two used DW-MRI, and one used TMS.

Some studies emphasized the role of the intact hemisphere. Analyzing G.Y., one of the most famous blindsight patients, (Bridge et al., 2008) demonstrated that in addition to the ipsilesional pathway from LGN to MT, which was similarly observed in control cases, two other projections also exist in G.Y.: a contralateral pathway from right LGN to left MT/V5 and a projection from the MT of the intact hemisphere to the MT of the injured hemisphere, created through interhemispheric connections. The study by (Tran et al., 2019) also pointed to the pathway that passes through hemispheres from ipsilesional SC to contralateral MT.

Five articles suggest that the higher cortical areas play a significant role in mediating blindsight. For example, (Tran et al., 2019) showed that in motion detection, the pathway passes from the ipsilesional SC to the contralateral MT and ipsilesional frontal area, suggesting a robust alternative route for visual processing. By incorporating the variable of awareness in the investigation of pathways leading to blindsight, (Sahraie et al., 1997) demonstrated that higher cortex regions can effectively create the phenomenon of blindsight. (Buetti et al., 2013) showed that in the stimulus detection task, the V1-bypassing pathway passes from SC to posterior dorsal areas. In the study by (Ptito et al., 1999), the patient performed a passive viewing task. The PET scan showed that the data passes from the pulvinar to the extrastriate cortex. In the study by (Benson et al., 1999), two tasks were performed: motion detection and direction discrimination, and the results suggested the pathway from tectopulvinar areas to extrastriate areas as the mediating pathway in blindsight.

Monkey studies

One article emphasized the role of the LGN to the extrastriate pathways in mediating blindsight. In a study by (Schmid et al., 2010), monkeys' brains were analyzed using fMRI during the rotating checkerboard

stimuli detection task. The results showed that in monkeys with V1 damage, the visual data passes through the LGN to the extrastriate pathway.

Four articles highlighted the importance of the SC-Pulvinar pathway. In a survey by (Kato et al., 2011), V1 was surgically removed by aspiration, and a visual detection task was conducted while fMRI images were taken from the monkeys' brains. The researchers identified two key pathways responsible for blindsight ability: SC to pulvinar and SC to LGN. The study rejects the role of LGN solely in blindsight. Another study (Isa, 2019) claimed that the main pathway for blindsight is the SC-Pulvinar-Extrastriate pathway. In a study by (Kinoshita et al., 2019), the monkeys' V1 areas were aspirated, and several months later, their brains were assessed histologically. The researchers recommended that the SC to the pulvinar pathway be responsible for blindsight. In a study by (Takakuwa et al., 2021), researchers claimed that the SC and pulvinar areas have a significant role in mediating blindsight as the pathway from SC to cortical areas through the pulvinar is the main pathway of blindsight. This article also claimed that LGN is an essential part of blindsight-mediating pathways.

Discussion

Blindsight continues to challenge traditional views of how vision is processed in the brain, particularly following damage to the primary visual cortex. This discussion integrates recent findings, emphasizes discrepancies among studies, proposes hypotheses to justify these discrepancies, and critically assesses the studies' methodologies to enhance our understanding of the pathways underlying blindsight.

Review of evidence regarding different blindsight pathways

The Spared V1 islands

The hypothesis that small, spared islands within the damaged V1 area contribute to blindsight is widely debated. Three studies support the role of spared V1 islands in blindsight (Morland et al., 2004; Papanikolaou et al., 2019; Radoeva et al., 2008). Two suggest these islands enable unconscious visual processing, using high-resolution fMRI to identify active V1 tissue (Morland et al., 2004; Papanikolaou et al., 2019). A potential weakness is the assumption that fMRI signals equate to functional processing, which may not always be accurate. Conversely, (de Gelder et al., 2008) and (Tran et al., 2019) provide evidence that blindsight can occur with complete V1 damage, questioning the necessity of V1 islands for residual visual function. The former used behavioral tests and anatomical imaging to demonstrate complete V1 damage, though minimal functional V1 tissue might still exist (de Gelder et al., 2008). Different imaging modalities could introduce inconsistencies in detecting small functional areas.

A hypothesis that might reconcile these findings is that while spared V1 islands can enhance certain blindsight types, their presence is not strictly necessary, and other neural mechanisms can effectively compensate for their absence. For example, in one study, the pathways responsible for blindsight are categorized based on the contrast of stimuli, showing that subcortical pathways ending in MT are the leading pathways for recognizing the high contrast stimulus in the impaired visual field. In contrast, the V1 is more efficient in recognizing low-contrast stimuli (Radoeva et al., 2008).

The LGN-Extrastriate pathway

The LGN to extrastriate cortex (also known as Geniculoextrastriate) pathway is increasingly recognized as crucial for blindsight. Studies show that direct pathways from LGN to MT are vital for the unconscious detection of movement in the damaged visual field (Ajina & Bridge, 2018, 2019; Ajina et al., 2015; Allen

et al., 2014; Bridge et al., 2010; Bridge et al., 2008). (Ajina et al., 2015) demonstrated this pathway's role using advanced neuroimaging, showing that direct LGN-MT connections are critical for motion detection without V1. (Ajina & Bridge, 2019) Used Diffusion-Weighted Imaging (DWI) and probabilistic tractography to map LGN-MT pathways, providing clear anatomical evidence. However, reliance on fMRI and DWI might not fully capture neural complexities, and the functional significance was inferred rather than directly tested in humans, which is a potential weakness. (Schmid et al., 2010) Validated these findings with precise lesion techniques and behavioral testing in monkeys, offering clear causal evidence. However, non-human primate studies may not directly apply to humans.

Although the experiment that (Allen et al., 2014) conducted using TMS-induced blindsight primarily favored the dominance of LGN-based pathways, it also indicates that the existence of other pathways—including tectopulvinar pathways—in creating blindsight is entirely plausible, suggesting that additional structures may be crucial. This argument is strengthened when we know that TMS's transient effects might not fully replicate chronic V1 damage. As we know, functional redundancy in the visual system ensures robust visual processing even when primary routes are compromised, so the discrepancy can suggest that the LGN-Extrastriate pathway is vital but works alongside other pathways, such as those containing the pulvinar and SC, to support blindsight.

The Superior Colliculus and pulvinar contributions

According to this hypothesis, pathways passing through the SC to the pulvinar, transferring information directly from the eye to regions above V1, play a significant role in the emergence of blindsight (Benson et al., 1999; Buetti et al., 2013; Ptito et al., 1999; Tran et al., 2019). Research by (Kato et al., 2011) and Isa (Isa, 2019) underscores the importance of the SC-based pathways in rerouting visual information after V1 damage. (Kato et al., 2011) conducted lesion studies in monkeys, using behavioral assessments and fMRI

to provide strong evidence for these pathways. However, generalizability to humans is uncertain due to species differences, and behavioral tasks in monkeys may not fully capture human visual processing complexities. (Isa, 2019) used reversible inactivation of the SC-pulvinar pathway in monkeys to show its role in blindsight, offering robust causal evidence. However, reversibility might not perfectly simulate permanent human lesions. Conversely, (Ajina & Bridge, 2018) argued that the SC-Pulvinar pathway alone is insufficient, emphasizing the need for LGN-Extrastriate cortex connectivity. They combined human neuroimaging and case studies to provide a comprehensive pathway overview, though reliance on correlational data limits causality inference. A methodological question is whether their imaging techniques detected all relevant subcortical activities. A hypothesis to reconcile these findings is that SC and pulvinar pathways act synergistically with the LGN-Extrastriate route, collectively supporting various aspects of blindsight. Individual differences in brain architecture and the nature of visual tasks performed could determine the relative contributions of these pathways.

The Intact hemisphere

The potential involvement of the intact hemisphere in compensating for V1 damage has been a subject of considerable debate. (Ptito et al., 1999) found that activation of extrageniculostriate pathways after damage to area V1 suggests the involvement of interhemispheric pathways. Some researchers concluded that the connection between the two hemispheres is a fundamental component in compensating for damage to V1 (Bridge et al., 2008; Celeghin et al., 2017; Papanikolaou et al., 2019; Tran et al., 2019). (Bridge et al., 2008) and (Celeghin et al., 2017) suggest that increased connectivity between the intact and damaged hemispheres contributes to blindsight. The former used DWI and functional connectivity analyses to show increased interhemispheric connections, providing strong anatomical and functional evidence (Bridge et al., 2008). A potential question is whether the observed connectivity changes directly result from V1 damage or pre-

existing conditions. The latter employed detailed case studies with advanced neuroimaging, offering a nuanced view of the intact hemisphere's role. However, the small sample size in case studies limits generalizability. On the other hand, some articles believe that the healthy hemisphere may not play a role in creating blindsight (Ajina et al., 2015; Bridge et al., 2010; Buetti et al., 2013). The study by (Ajina et al., 2015) downplays the intact hemisphere's role. This study emphasizes direct LGN-MT pathways, suggesting that interhemispheric connectivity may not be as critical. This study claims blindsight relies on functional connections between MT and LGN, not interhemispheric connections. A methodological question is whether their imaging techniques could detect subtle changes in interhemispheric connectivity. This discrepancy might be justified by proposing that the intact hemisphere's contribution varies depending on the specific visual tasks and the extent of interhemispheric communication established through neuroplasticity. Pre-existing individual differences in brain lateralization and connectivity may also influence the degree of compensation by the intact hemisphere.

Role of higher-order cortical areas

A study (Ajina & Bridge, 2018) used neuroimaging to show that blindsight depends on an operational link between the MT and the LGN, not the pulvinar, suggesting the involvement of higher-order cortical areas. This study provides robust anatomical evidence, though the correlational data limits causality. (Bridge et al., 2010) identified extrastriate cortex activation without V1 activation, highlighting the role of higher cortical areas in visual processing. This study demonstrates the involvement of the higher-order regions using fMRI. Contrary to these articles, (Sahraie et al., 1997) emphasized the role of subcortical pathways, suggesting that higher-order areas may not be necessary for all aspects of blindsight.

Cooperative pathways

As said earlier, G.Y. is probably the most well-known case of blindsight, which has been extensively tested. Numerous studies on this individual provide a unique picture of the simultaneous activities of multiple pathways in creating blindsight. Two articles identify the SC-Pulvinar pathway as the main route for affective blindsight in G.Y. (de Gelder & Hadjikhani, 2006; Van den Stock et al., 2011). Studies by (Bridge et al., 2008) and (Celeghin et al., 2017) highlight the role of the intact hemisphere in blindsight, with the former noting increased thalamocortical (e.g., LGN to MT) and corticocortical (e.g., MT/V5 between hemispheres) connections in G.Y. The presence of articles proposing different pathways in G.Y. suggests that multiple blindsight pathways can simultaneously be activated in one person. (Papanikolaou et al., 2019) concluded that residual blindsight abilities might result from fine coordination between residual V1 areas and MT and connections from SC and LGN areas to MT, confirming the presence of multiple pathways in damaged individuals. An explanation is that some of these pathways could potentially develop after brain injury, adding to previously existing ones that did not emerge due to the dominance of the primary visual system, becoming active only after V1 damage. The presence of older pathways, alongside those that form after an injury, can result in more than one pathway being active simultaneously in an individual. In some cases, these pathways may cooperate and overlap with each other.

Human and animal study parallels

The articles that studied blindsight in monkeys also arrived at more or less similar results in humans. Among animal studies, the first group emphasizes SC's significant role in creating blindsight, particularly the pathway from SC to pulvinar (Kato et al., 2011; Kinoshita et al., 2019; Takakuwa et al., 2021). (Schmid et al., 2010) support the involvement of the LGN-Extrastriate pathway in monkeys. Human studies frequently utilize non-invasive imaging and correlational methodologies, offering valuable insights, although lacking

the experimental rigor seen in animal research. Discrepancies, such as a heightened focus on SC-Pulvinar pathways in animals against a more equitable consideration of LGN and SC contributions in humans, may be ascribed to species-specific variances in visual processing or methodological disparities. A suggestion to explain this mismatch is that, whereas core pathways are preserved across species, the dependence on individual channels may vary due to evolutionary adaptations and differences in cortical complexity between humans and animals.

Causes of differences in blindsight pathway activation

The activation of blindsight pathways can differ significantly among individuals due to several factors discussed below.

Individual variability in neuroanatomy

Brain structure and connectivity variations can lead to individual differences in pathway activation. Certain studies suggest structural variations in the areas associated with blindsight pathways among people (Bridge et al., 2008), potentially influencing the efficacy of each pathway in compensating for V1 loss. The structural variations may result in discrepancies in the activation of several cortical and subcortical circuits.

The extent of V1 damage

The severity and exact location of the lesion in the V1 region can influence the routes employed for blindsight. The residual functionality in V1 may lead to differing degrees of pathway activation, affecting the extent of blindsight. (Ajina & Bridge, 2018) showed that individuals with residual V1 function effectively utilize direct pathways from the LGN to higher visual areas like the MT region. Functional V1 remnants may influence the balance between cortical and subcortical pathway use.

Age at the time of injury and time elapsed since injury

The significance of time is well-established; however, examining its impacts presents difficulties. While acknowledging the importance of time can improve our comprehension of the brain's adaptive functions post-V1 loss, the variety in individual recovery rates, disparities in the severity of V1 damage, and methodological inconsistencies among studies can mislead interpretations.

The active pathways are strongly influenced by the age at which the V1 injury happens, suggesting that different pathways are preferred in younger brains compared to older ones and that these preferences change with time. Increased neuroplasticity in developing brains makes it easier for young children to rewire their visual circuits. A study by (Celeghin et al., 2017) highlights that younger patients with stronger neuroplasticity can create more robust compensatory networks, allowing them to maintain some visuomotor functions even after severe damage to critical visual areas. This group of patients exhibited enhanced visual information transmission due to enhanced transcallosal connections between their unaffected and damaged hemispheres. While still capable of some neuroplastic adaptation, it is possible for older brains to show a different pattern of compensatory mechanisms due to reduced plasticity.

The time elapsed since a V1 lesion is another critical factor in the emergence of blindsight abilities. Longitudinal studies, detailed case analyses, and animal research all highlight that neuroplastic changes occur gradually and require significant time to manifest fully, so the patients assessed soon after the injury may show different activation patterns than those evaluated after a more extended period, reflecting ongoing neuroplastic changes. Studies conducted immediately after the T.N. injury indicated limited blindsight capabilities, whereas follow-up studies years later revealed much more pronounced visual functions. In a study by (Andino et al., 2009), conducted shortly after T.N.'s bilateral V1 damage, it was suggested that the LGN to extrastriate areas to the amygdala pathway is the main route for affective blindsight, questioning the direct SC-Pulvinar-Amygdala route. However, another study (Burra et al., 2019) on T.N. eight years post-injury suggested the SC-Pulvinar-Amygdala pathway is the main route for affective blindsight. This

discrepancy may be due to neuroplasticity, providing T.N. with a new pathway absent at the time of injury. This further substantiates the concept that fundamental blindsight pathways may be replaced over time and that the brain's compensating mechanisms necessitate significant time for complete development. Animal studies further support the significance of temporal factors in the development of blindsight. (Kinoshita et al., 2019) performed research on monkeys with V1 lesions and discovered that alternative visual pathways, including the SC-Pulvinar-Extrastriate route, progressively gained prominence during the months following the injury. The gradual enhancement in route functionality aligns with the documented neuroplastic alterations in human research, suggesting that temporal factors are essential in humans and non-human primates. These findings underscore the dynamic characteristics of neuroplastic adaptation and the significance of individualized strategies dependent upon the patient's age and duration since injury in the management and rehabilitation of blindsight.

Cognitive and attentional states during the test and the stimulus type

We should not easily overlook the potential impact of experiment conditions on the traced pathways. Individuals' cognitive and attentional states can influence the activation of blindsight pathways. (Ptito et al., 1999) discovered that attentional states can affect the processing of motion. In a patient, (Buetti et al., 2013) demonstrated a distinction between goal-directed and discrete response localization, suggesting that the activation of specific pathways is significantly influenced by cognitive burden and attentional focus. However, the solitary case study restricts generalizability. (Sahraie et al., 1997) discovered that neural activity patterns linked to conscious and unconscious processing of visual stimuli fluctuate with cognitive and attentional states, influencing the preferred utilization of specific pathways.

The type of visual stimuli, especially those loaded with emotional content, might variably activate blindsight circuits. (Pegna et al., 2005) demonstrated that affective blindsight, represented by the non-

conscious processing of frightening facial expressions, primarily involves the SC-Pulvinar-Amygdala pathway, as indicated by heightened activation of the right amygdala. This suggests that emotionally charged inputs may selectively activate specific subcortical pathways associated with affective processing.

The implications of neuroplasticity for rehabilitation

After considering all of these variables, it is possible to infer that neuroplasticity plays a substantial role in blindsight following an injury to the V1 region. Pre-existing pathways may account for initial forms of blindsight, but substantial neuroplastic alterations over time might markedly enhance and fortify these capabilities (Figure 2). The potential for neuroplasticity and the reorganization of neural circuits is likely affected by genetic variations, the age at which injury occurs, and the extent of the damage.

Highlighting the roles of the LGN-Extrastriate and SC-Pulvinar pathways, these findings significantly impact clinical interventions to enhance visual functionality in patients with V1 damage. From a therapeutic point of view, blindsight mediating pathways can serve as targets for rehabilitation strategies. For example, targeted therapies that activate the SC-Pulvinar route could help enhance emotional and spatial awareness, particularly in patients with affective blindsight, and targeted visual training programs focusing on motion detection tasks may stimulate the LGN to MT pathway, improving patients' ability to detect motion in the blind field. Having comprehended the importance of repetitive practice and targeted interventions in fostering neuroplasticity, it is evident that both short-term and long-term strategies are crucial for optimizing rehabilitation efficacy. The best practical therapy approach may be one that integrates multiple perspectives. Cross-modal sensory stimulation, such as combining auditory or tactile cues with visual tasks, can also leverage cross-modal plasticity to aid visual processing. By stimulating multiple sensory pathways, rehabilitation can enhance the brain's adaptive mechanisms, reinforcing the neural circuits involved in

blindsight. These clinical interventions offer a promising avenue for restoring vision or improving visual tasks, enhancing patients' independence and well-being.

Recent data underscores the diversity and plasticity of the visual system, indicating that numerous mechanisms may facilitate blindsight. Although spared V1 islands may contribute to this phenomenon, the LGN-Extrastriate, and SC-Pulvinar pathways are increasingly recognized as critical pathways for residual visual function. While also introducing diversity in the manifestation of blindsight, the brain's adaptability and the potential involvement of the intact hemisphere enhance our comprehension while also introducing variety in the manifestation of blindsight. The age at which a V1 injury occurs and the time since the injury are critical in identifying the neural pathways associated with blindsight. The findings underscore the dynamic characteristics of neuroplastic adaptation and the significance of individualized strategies in managing and rehabilitating blindsight. To enhance the recovery of individuals with cortical blindness, future research should explore these pathways in rehabilitation protocols, potentially integrating neuromodulation, visual retraining, and cross-modal sensory stimulation to activate residual pathways and enhance adaptive neuroplastic responses. By advancing our understanding in these fields, we can create more effective rehabilitation strategies that will ultimately leverage the brain's inherent plasticity to restore vision.

Due to the low prevalence of blindsight, most articles are case reports involving a few patients, such as G.Y. and T.N., whose data is often repeated, potentially biasing our understanding of alternative pathways. While providing detailed insights, small sample sizes and case reports may not be generalizable to larger populations and are limited by their anecdotal nature and lack of control groups. Particular research lacked specificity about the characteristics of V1 lesions, impeding repeatability and systematic comparisons. Furthermore, our data was inappropriate for meta-analyses, and all human investigations were retrospective, hindering our ability to monitor individual variations in most instances. The investigations utilized a variety of methodologies, such as imaging modalities (fMRI,

EEG, PET, DW-MRI) and behavioral activities, which hindered the ability to make definitive conclusions about blindsight pathways. Future research should prioritize longitudinal studies to track pathway activation over time. Such studies would allow for a deeper understanding of compensatory mechanisms as they evolve, enhancing our knowledge of long-term visual recovery. Standardizing methodologies—including consistent imaging techniques and outcome measures—would also improve comparability across studies. Expanding sample sizes could further strengthen statistical reliability and enhance the generalizability of findings.

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Ethical Consideration

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Iran University of Medical Sciences.

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Authors' contribution

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Conceptualization: A, B, C, D, E/ **Methodology:** A, B, C, D, E/ **Investigation:** A, B, C, D, E/ **Writing - Original draft:** A, D, E/ **Writing – Review & Editing:** A, B, C, D, E, F/ **Funding Acquisition and Resources**: F/ **Supervision:** E, F

The manuscript has been read and approved by all authors, and all authors agree to submit the manuscript to the Journal. This article has not been submitted for publication to other publications or published elsewhere.

Conflict of interest

It is important to acknowledge that Dr. Joghataei, the author of this article, is the Editor-in-Chief of the BNC journal. No other conflicts of interest exist.

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Table 1. Human studies data

o.	**thor**			**pe**	**ntrol)**	**ntrol)**	**ntrol)**
			nd	ort			
				ort			
	& Hadjikhani			ort			
				ort			
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				trol			1M
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				ort			
	laou			trol		-65	M/4F and 1M
				trol		-61	M/3F and 2M
	Bridge			trol		2/50.1±14.6	0M/Not Mentioned
	Bridge			trol		53.2±12.1	M/3F and 5M
				trol	indsight positive)/9	9±11.7	2M/3F and 6M
				es	luded)/0	4/-	M/ -
				trol		1.8±2.5	ioned
				trol			1 4M
				trol		5.1	entioned

Information regarding the first author of the articles, year of publication, country, study type, and demographic characteristics of the cases and controls

Table 2. Injury data of subjects of Human studies

	Mechanism **acy)**	**ocation As Mentioned In Article/ (Unilateral/Bilateral)**	**nset Age**	**ent Time** **apsed Since**
		A: Left parietal, temporal, and occipital area; VA: Right posterior areas/ Bilateral		fter the first & fter the second
		visual cortices/ Bilateral		
		e cortex/ Unilateral		
		rtices/ Bilateral	ioned	ioned
	1)	e cortex/ Unilateral		
	-Asphyxia (1)	ccipital areas/ Bilateral		
	1)	al cortex/ Unilateral		
	1)	pital lobe/ Unilateral		
		rtex/ Bilateral		
	1)	etal and medial occipital lobe/ Unilateral		
		al occipital lobe/ Unilateral		
		3 Patients) – Right V1 (2 Patients)/ All Unilateral	ioned	es 7 y – 10 y – 6 months
	- Trauma (1) - - Surgery (1) -)	dial and lateral occipital (3 Patients) – al cccipital (3 Patients) – Left lateral occipital + iation (1 Patient) – Right medial occipital (1 Patient)/ All Unilateral	verage	verage
	) - Surgery (1)	teral	ioned	nths
	event of origin (1) 7)	al And Bilateral	6 months nt)	months
	) - Surgery (1)	teral	ioned	nths
	uced (16)	lobe/ Not Mentioned	y he nt)	y he experiment)
	event	matter of V1		

	wn origin (4)	uring of V1 at the anterior tip of the calcarine sulcus)/ Bilateral		
	1)	al occipital lobe & Right parietal lobe/ Bilateral		
	1)	e cortex/ Unilateral		

Information regarding the mechanism, location, and time of the injury, as well as the time elapsed since it occurred

Table 3. Assessments of blindsight pathways in Human studies

	ed	**Used**	**g or Imaging Type/ es**	**l Blindsight Pathways**
	iewing	f angry, happy, d neutral faces	- 125 Electrodes	**rmation:** Pathways from the Extrastriate Cortex Anterior areas and finally ended in the Amygdala **xtrastriate Pathways)** **tion:** A probable direct SC-Pulvinar-Amygdala
	iewing	f fearful and neutral faces		**nar-Amygdala**
	discrimination	f happy and neutral whole ression with blurred faces	T	y body images: **SC–Pulvinar–MT** expressing fear: **SC–Pulvinar**
	discrimination	f angry, happy, neutral, l faces	5 T	expressions, especially fear: **nar-Amygdala route** complex emotional scenes: **n of Cortical visual areas** before lala response
	discrimination	f angry and neutral l whole-body actions	T	**nar to the bilateral Amygdala**
	iewing	djacent sinusoidal	Mentioned	**geniculostriate** pathway involving the V3
	discrimination	fast-moving dots	5 T	re (slow) mode: Mostly subcortical; **ht medial and orbital frontal area** (fast) mode: Mostly cortical; ral prefrontal, may with **ispheric connections**
	etection	lots	T	**mation:** Ipsilesional **SC**, contralateral **MT**, esional frontal areas **tion:** Role of spared V1 islands
	etection	ite circles	ot Mentioned	terior dorsal regions (including the parietal cortex) ior motor areas **ner Cortex Pathways)**
	etection and	tic grating varying	oked potential (VEP)	**vinar-Extrastriate**

	discrimination	nce contrast	ntioned	**ner Cortex Pathways)**
	1. Detection of the onsets/offsets of moving and stationary stimuli 2. Detection of moving stimuli of variable contrasts 3. Detection of motion direction 4. Shape and color discrimination	g or stationary ave gratings ntric rings with ferent levels of contrast (moving in or out) , triangles, s all black on white nd/ Red, blue, or cles on a white background		**tion:** The role of **spared V1 islands** and also jections from subcortical areas in activating **ortical areas** based on contrast levels. ontrast level subcortical pathways to MT in addition to an attenuated V1 input, are for MT activation but in a lower contrast pathway may be predominant)
	nge detection	quare-checkerboard bars ging color (red to green)	T	**rmation: Spared V1 islands to MT pathways** in company with **SC-Pulvinar-MT** or **LGN-MT** and also the possible role of MT in the intact ere
	discrimination	grating stimuli	5 T	**rmation:** Role of **spared V1 islands** V1-bypassing pathways
	(onset) n and discrimination	moving black dots	T	**rmation: LGN to (Ipsilesional) MT** pathways **tion:** Sufficiency of SC-Pulvinar pathway
	iewing	chromatic tch in 5 contrast levels	T	**MT**
	iewing	chromatic Gabor patch rast levels	/ High Angular n Diffusion Imaging) Probabilistic aphy	**MT**
	and detection	f arrows in different es and directions	**ng is done** vice: Magstim Super hasic stimulator action with m high-power und coil	**rmation:** **GN projections** **tion:** Retinotectal pathways

	us detection liscrimination detection zation ction tasks	patch of blue or yellow objects m dot kinematograph n 10 × 10 white square	erfusion Imaging + Echo-Planar (GRE-EPI)/ 3 T	**Ipsilateral) MT**
	iewing and nt detection	nd stationary dots	stic Tractography -MRI/ 1.5 T	cortical (between LGN misphere and MT/V5 in the other) icocortical connectivity of MT/V5 between emispheres **xtrastriate Pathways** **of Intact Hemisphere)**
	onset detection	quare against a dark nd	DTI/ 3T	**mation:** The role of **intact hemisphere** in transferring data from ipsilesional Extrastriate the contralesional homologous area)

Information on the methodology of blindsight assessment, including the type of task, type of stimuli, tools used, and proposed pathways (LGN: Lateral Geniculate Nucleus, SC: Superior Colliculus, MT: Middle Temporal, DW-MRI: Diffusion-Weighted MRI, TMS: Transcranial Magnetic Stimulation)

Table 4. Monkey studies data

	thor				ype	ntrol)	ntrol)	ntrol)
				hulatta	tudy		lature	F/F
				monkeys		ioned	ioned	ioned
				uscata	tudy		ioned/ -	F/-
				uscata and hulatta	tudy		ioned/ ioned	entioned
	a			fuscata	tudy			

Information regarding the first author of the articles, year of publication, country, study type, and characteristics of the animals

Table 5. Injury data of subjects of Monkey studies

	y Mechanism	**ocation (Unilateral/ Bilateral)**	**nset Age**	**ent time (Time Elapsed Since Injury)**
	y removed by Aspiration	in female and Left le case/ Unilateral	ioned	ioned
	ioned	ateral	ioned	ioned
	y removed by Aspiration	U: Right V1/ A: Left V1/ Unilateral	ioned	s in Monkey A and s in Monkey U
	y removed by Aspiration	C and H: Right side/ A: Left side/ Unilateral	ioned	s in Monkey C onths in Monkey H
	y removed by Aspiration	Unilateral	ioned	ns in Monkey O and nths in Monkey T

Information regarding the mechanism, location, and time of the injury, as well as the time elapsed since it occurred

Table 6. Assessments of blindsight pathways in Monkey studies

	ed	**Used**	**g or Imaging Type**	**l Blindsight Pathways**
		checkerboard	ot Mentioned	**trastriate**
	guided detection)	muli	ests (No Imaging)	**nar-Extrastriate**
	guided detection)	muli	al Tests (Ability to localize stimuli - No Imaging)	**rmation:** The role of **inar** and (possible ment of) **SC-LGN pathways** **tion:** The LGN sufficiency
	guided detection)	muli	al Tests (Ability to localize stimuli) ogical Assessment	**nar pathways**
	guided detection)	muli	al Tests (Ability to localize stimuli - No Imaging) ogical Assessment	**rmation:** **nar-Higher Cortex** **s and LGN's role**

Information on the methodology of blindsight assessment, including the type of task, type of stimuli, tools used, and proposed pathways (LGN: Lateral Geniculate Nucleus, SC: Superior Colliculus)

Figures

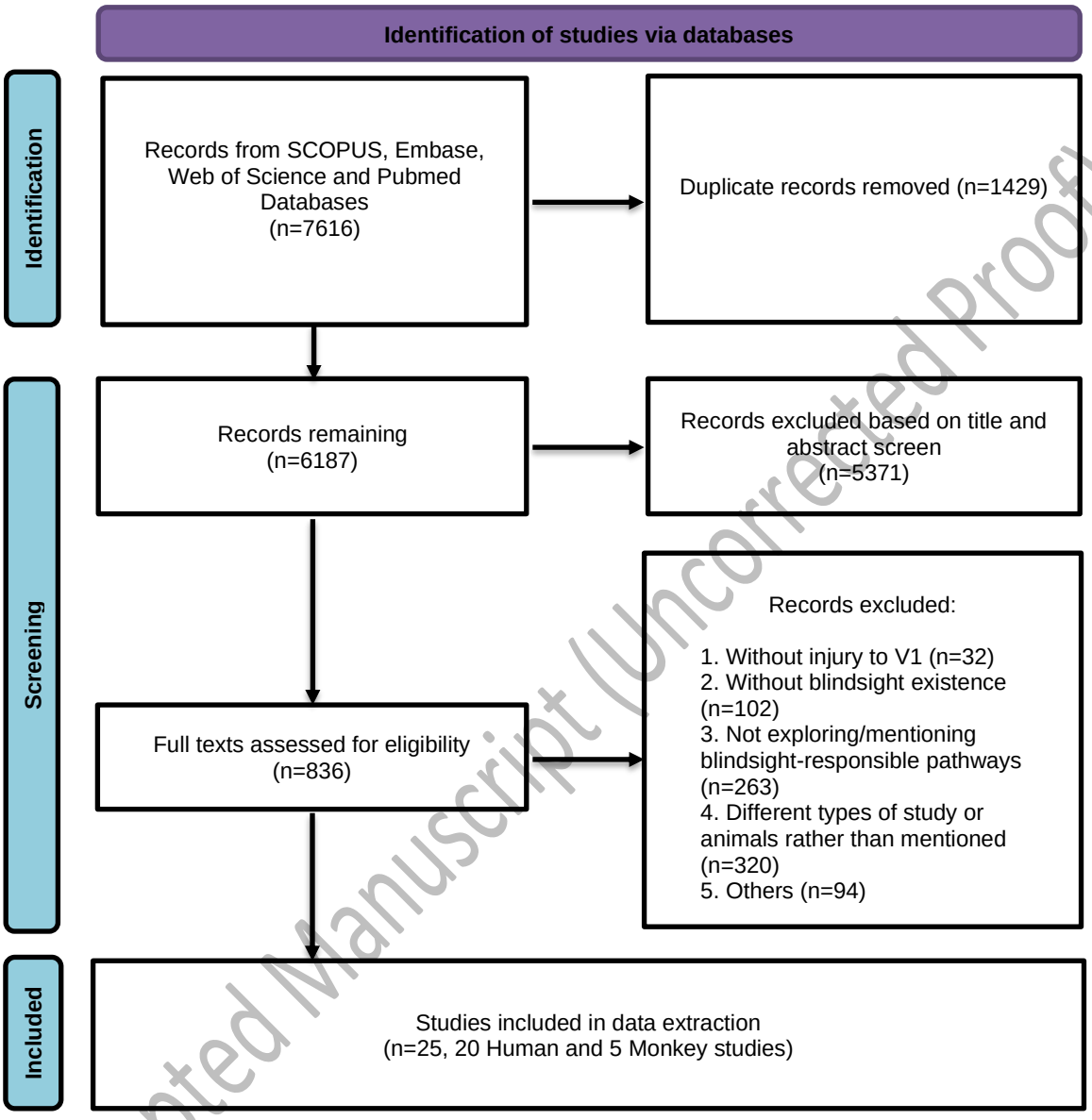

Figure 1: The process of selecting the eligible articles.
The exact number of chosen articles in each section and the reason for exclusion are provided

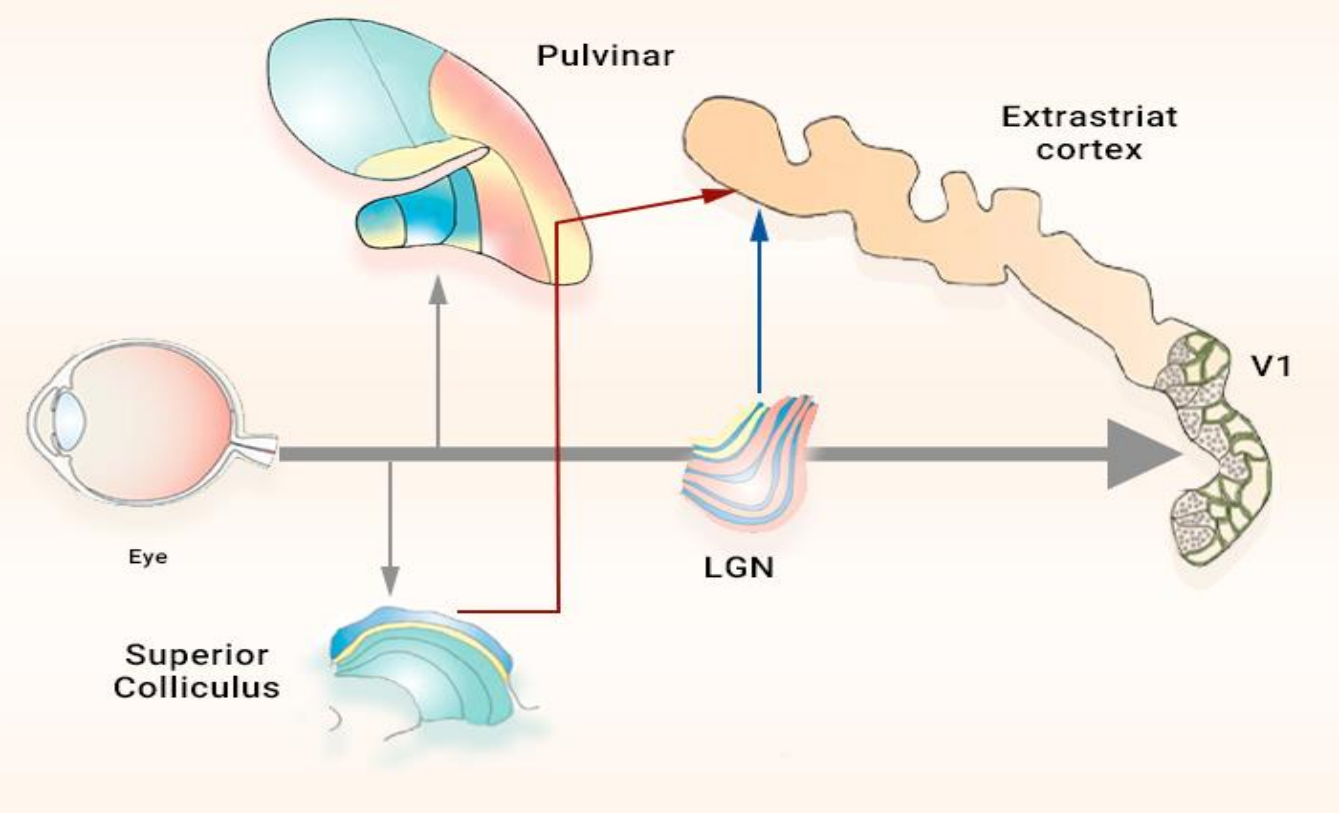

Figure 2: Pathways that facilitate blindsight (Red, Blue, and Green arrows).
Gray arrows show the main path in normal brain (LGN: Lateral Geniculate Nucleus)

Supplements

Search Strategy

Pubmed: (Blindsight OR “Blind sight” OR ((residual OR unconscious) AND vision)) AND ("Calcarine” OR “Brodmann17” OR “v1” OR "visual area I" OR "area 17" OR "area striate" OR ((first OR early OR primary) AND (visual OR vision)) OR ((Cortex OR Cortices) AND (Visual OR vision OR striat*)))

SCOPUS: (Blindsight OR “Blind sight” OR ((residual OR unconscious) W/2 vision)) AND ("Calcarine” OR “Brodmann 17” OR “v1” OR "visual area I" OR "area 17" OR "area striate" OR ((first OR early OR primary) W/2 (visual OR vision)) OR ((Cortex OR Cortices) W/2 (Visual OR vision OR striat*)))

Web of Science: (Blindsight OR “Blind sight” OR ((residual OR unconscious) NEAR/2 vision)) AND ("Calcarine” OR “Brodmann17” OR “v1” OR "visual area I" OR "area 17" OR "area striate" OR ((first OR early OR primary) NEAR/2 (visual OR vision)) OR ((Cortex OR Cortices) NEAR/2 (Visual OR vision OR striat*)))

Embase: (Blindsight OR “Blindsight” OR ((residual OR unconscious) NEAR/2 vision)) AND ("Calcarine” OR “Brodmann17” OR “v1” OR "visual area I" OR "area 17" OR "area striate" OR ((first OR early OR primary) NEAR/2 (visual OR vision)) OR ((Cortex OR Cortices) NEAR/2 (Visual OR vision OR striat*)))