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Right inferior longitudinal fasciculus lesions disrupt visual-emotional integration

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Abstract

The mechanism by which the brain integrates visual and emotional information remains incompletely understood, and can be studied through focal lesions that selectively disrupt this process. To date, three reported cases of visual hypoemotionality, a vision-specific form of derealization, have resulted from lesions of the temporo-occipital junction. We present a fourth case of this rare phenomenon, and investigate the role of the inferior longitudinal fasciculus (ILF) in the underlying pathophysiology. A 50-year-old right-handed male was found to have a right medial temporal lobe tumor following new-onset seizures. Interstitial laser ablation of the lesion was complicated by a right temporo-parieto-occipital intraparenchymal hemorrhage. The patient subsequently experienced emotional estrangement from visual stimuli. A lesion overlap analysis was conducted to assess involvement of the ILF by this patient's lesion and those of the three previously described cases, and diffusion tensor imaging was acquired in our case to further investigate ILF disruption. All four lesions specifically overlapped with the expected trajectory of the right ILF, and diminished structural integrity of the right ILF was observed in our case. These findings implicate the ILF in visual hypoemotionality, suggesting that the ILF is critical for integrating visual information with its emotional content.

Key words: dissociative disorders; derealization; emotions; visual hypoemotionality

Introduction

To generate a coherent sense of reality, the brain must bind perceptual experiences to emotional qualities, though the neuroanatomical structures necessary for this integration remain incompletely understood. By interfering with this process, dissociative experiences such as derealization (the experience of estrangement from the external world) offer unique insights into the neurobiology of sensory-emotional integration. Neuroimaging studies of dissociation have demonstrated that right-lateralized temporal and parietal cortices may be important sites for multisensory integration and perceptual awareness (Simeon *et al.*, 2000). Cases of secondary derealization following temporal lobe epilepsy and focal lesions of the temporal lobe

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further implicate the temporal lobe in the perceptual integration of reality (Lambert *et al.*, 2002).

Dissociation can be specific to a particular sensory modality, such as nociception or vision, and is most frequently appreciated in the latter (Sierra and Berrios, 1998). The three cases of lesion-induced vision-specific derealization reported to date have been characterized by visual hypoemotionality, whereby visual stimuli lack emotional valence (Bauer, 1982; Habib, 1986; Lopera and Ardila, 1992; Sierra *et al.*, 2002). This diminution of emotional responsivity, sometimes termed de-affectualization, likely contributes to the apparently inauthentic quality of reality characteristic of derealization (Medford, 2012). The lesions that caused the three previously reported cases of visual hypoemotionality have all involved the temporo-occipital junction: in the first reported case, a 39-year-old right-handed man suffered bilateral intraparenchymal hemorrhages of the posterior temporal lobes following head trauma from a motorcycle accident (Bauer, 1982), the second case described a 71-year-old woman who suffered a right temporo-occipital infarct (Habib, 1986), and the third described a 58-year-old man who developed bilateral intraparenchymal hemorrhages of the temporo-occipital regions following head trauma from a motor vehicle accident (Lopera and Ardila, 1992; Sierra *et al.*, 2002). All three patients subsequently developed visuospatial deficits, prosopagnosia and left visual field deficits, but most notably, visually specific hypoemotionality. The first described natural scenery as dull, and cancelled his subscription to an adult magazine after no longer finding the images erotic. The second, a gardener, could no longer appreciate the beauty of her flowers. The third described landscapes as appearing artificial and plastic, lacking their usual beauty. These instances suggest that the neural circuits underlying sensory-emotional integration are divisible into sensory-specific components, and that visual hypoemotionality may result from dysfunction of neural circuits connecting the occipital and temporal cortices. The inferior longitudinal fasciculus (ILF), a major tract between the extrastriate visual association cortex and the temporal lobe, may be a critical structure mediating this communication, though it has not yet been clearly implicated in visual hypoemotionality (Bauer, 1982; Catani *et al.*, 2003).

Here, we describe a case of a patient with an ablated right medial temporal tumor and right temporo-parieto-occipital hemorrhage, who developed visual hypoemotionality. We tested the hypothesis that this phenomenon is associated with ILF injury. We performed the first lesion overlap analysis of lesional visual hypoemotionality, comparing this case's lesion with those from previously published cases, and assessed their overlap with the ILF. We also used diffusion tensor imaging (DTI) to investigate whether this patient's lesion was associated with diminished structural integrity of the ILF or interhemispheric fibers.

Case report

A 50-year-old right-handed Caucasian male presented to the emergency department following a witnessed secondarily generalized tonic-clonic seizure. Immediately prior to this event, he reported an intense *déjà vu* experience followed by the perception of viewing a co-worker's skin as if through a magnifying glass. Past medical/neuropsychiatric history was notable for several remote episodes of head trauma with loss of consciousness, prior alcohol misuse and a distant episode of depression in the context of psychosocial stressors.

On presentation, his neurological exam was normal. Brain magnetic resonance imaging (MRI) revealed a right medial temporal lobe T1-hypotense, T2-hyperintense non-enhancing lesion (Supplementary Figure S1). Subsequent stereotactic biopsy revealed a dysembryoplastic neuroepithelial tumor (World Health Organization Grade I). He did not tolerate multiple antiepileptic drugs, and so was evaluated for epilepsy surgery. Electroencephalogram (EEG) off of medications revealed interictal right temporal epileptiform discharges and captured a secondarily generalized right temporal onset seizure.

The patient was presented with surgical options, and selected MRI-guided lesional thermal ablation. The laser probe was placed into the mesial temporal lobe lesion via a stereotactic parietal approach. Imaging following the ablation but before removal of the probe showed the expected lesion at the site of the ablation and did not demonstrate any hemorrhage. Immediate post-operative neurologic examinations revealed no new neurological deficits. Ten hours post-operatively, the patient was found to have a left homonymous hemianopsia (Figure 1A). Computed tomography and MRI showed a right posterior temporo-parieto-occipital intraparenchymal hemorrhage not present on the post-ablation scan (Figure 2, Supplementary Figure S2). He was treated conservatively, maintained on oxcarbazepine, and discharged home with outpatient occupational and visual therapy. His left visual deficit gradually improved over the next 10 months (Figure 1B).

Following discharge, the patient experienced 1–2 weeks of modest difficulty interpreting facial expressions. He also developed difficulty with visuospatial navigation and short-term memory, as demonstrated by pre- and post-surgery neuropsychological testing (Supplementary Table S1). Most strikingly, he noted a 'sense of visual estrangement', which became increasingly apparent as his visual field deficit resolved over the 2–3 months following surgery. He felt his surroundings did not 'feel real', which he attributed to a sense of emotional disconnectedness from his visual perceptions. He reported seeing loved ones without feeling the expected emotions. He described this phenomenon as specific to vision, without feeling similarly estranged while conversing with or embracing loved ones. His visual hypoemotionality was reflected by an increase in his Dissociative Experiences Scale-II total score (Carlson and Putnam, 1993), which rose from 20 at his pre-surgical assessment to 30 following his hemorrhage (Supplementary Table S1). This rise was significant according to the Reliable Change Index, a calculation that uses test–retest reliability and the standard deviation of the population sample to determine if a change exceeds expected random variability (Christensen and Mendoza, 1986). The quantitative rise in his Dissociative Experiences Scale-II total score, which was driven largely by an increase in the depersonalization/derealization factor from 20 to 54, suggests that his derealization was attributable to his injury and not to a pre-morbid condition.

Post-operatively, the patient endorsed mild dysphoric mood attributed to changes in professional and social functioning. However, his Beck Depression Inventory–II scores actually improved from 32 pre-operatively to 18 post-operatively (Supplementary Table S1). He denied Capgras delusions (i.e. though he felt emotionally disconnected from others, he did not interpret them as imposters), and other psychotic spectrum, anxiety or alcohol/drug misuse symptoms/behaviors. His visual estrangement continued for $\sim$10 months and occurred intermittently thereafter (particularly with fatigue). He also developed a post-operative episode of a suspected simple partial seizure (bright orange-red dot in his left visual field) that was well

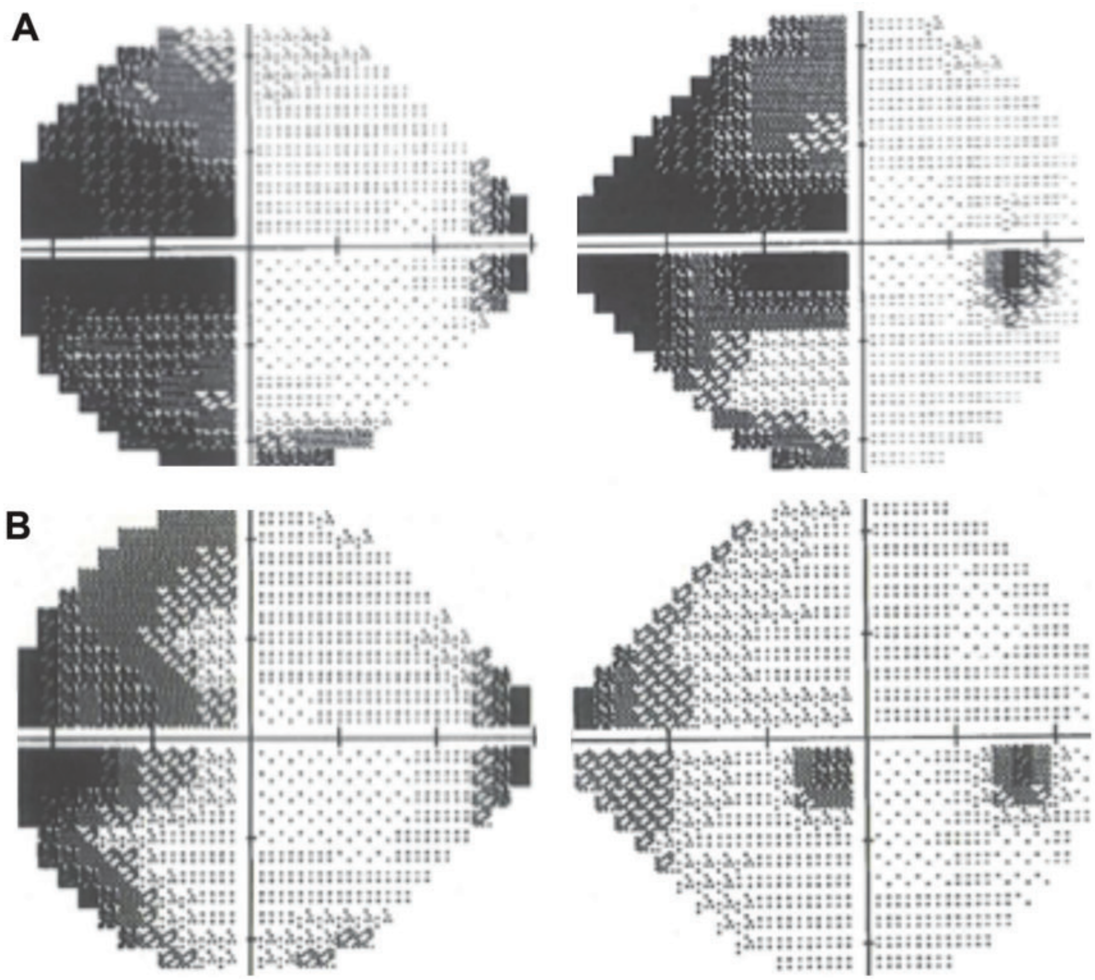

Fig. 1. Visual field analyses of left visual field deficit. Analyses conducted 1 month (A) and 11 months (B) following the intraparenchymal hemorrhage demonstrate improvement in visual deficit.

controlled with a dose increase of oxcarbazepine. An outpatient EEG performed while the patient experienced constant visual estrangement symptoms did not demonstrate any appreciable epileptiform activity, as interpreted by a board-certified epileptologist. A subsequent 48-h inpatient video-EEG, which captured an event wherein the patient reported a 'bizarre feeling' and 'inability to see properly', also did not show appreciable epileptiform activity.

Materials and methods

Comparative lesion tracing

A lesion overlap analysis was performed to investigate the brain regions common to the patient's lesion and those from three prior cases of lesional visual hypoemotionality (Bauer, 1982; Habib, 1986; Lopera and Ardila, 1992). To normalize the four lesion images to a standardized brain, axial views of each lesion (either from the patient's MRI or from axial images in the previous case reports) were reproduced on comparable axial views of a template brain in Montreal Neurological Institute space available through Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) (Jenkinson *et al.*, 2012), guided by neuroanatomical landmarks. To approximate the three-dimensional (3D) extent of the lesions, the axial images of each lesion were viewed in each sagittal plane, the edges of the two-dimensional images were adjoined by straight lines and the resulting lesion outlines were filled in, producing a 3D volume. We validated this method by comparing the resulting sagittal lesion views to the actual sagittal MRI views of our patient's hemorrhage, which were notably similar (Supplementary Figure S3). Lesion reproductions and 3D transformations were performed by D.B.F and reviewed for accuracy by A.D.B. For independent validation, a third previously trained evaluator who was blinded to the clinical information of the cases and to the hypothesis of the study repeated the lesion reproductions and 3D transformations. Once all four lesions had been reproduced in 3D, the lesions and the right ILF were superimposed. The ILF was defined by the Johns Hopkins University white-matter tractography atlas within FSL (thresholded at 5; Hua *et al.*, 2008).

DTI tractography

DTI was collected in the present case to compare the structural integrity of the ILF of the right (lesioned) hemisphere to that of the left hemisphere. DTI images were acquired ~2 years following symptom onset, when visual hypoemotionality continued to occur intermittently. DTI was acquired with 20 gradient directions (TR = 3700, TE = 95, b-value = 1000) using a 3 tesla MR unit equipped with a 20 channel head coil (Siemens Skyra,

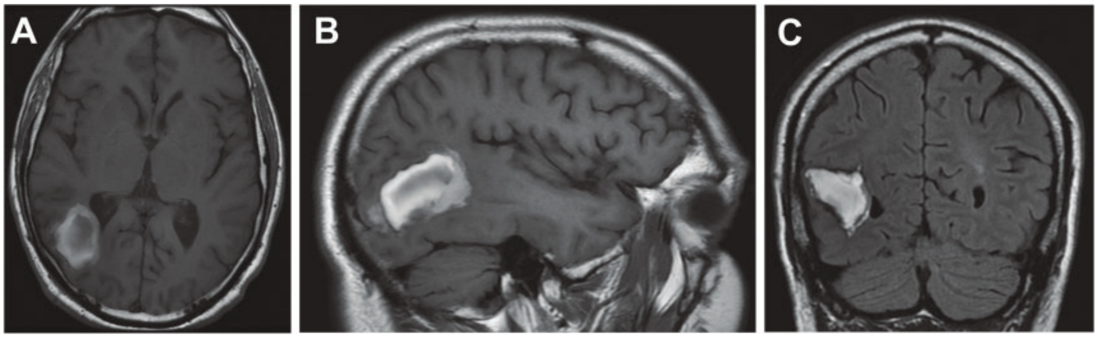

Fig. 2. The post-surgical hemorrhage appeared as a $3.7 \times 2.6 \times 3.3$ mm right posterior temporo-parieto-occipital intraparenchymal hemorrhage on T1 MRI (A, B), and on T2 Fluid Attenuated Inversion Recovery (FLAIR) MRI (C). Note: All images are displayed using radiologic convention.

Siemens healthcare, Erlangen, Germany). Whole brain single tensor unscented Kalman filter tractography (Malcolm *et al.*, 2009) was performed followed by tract selection in 3D Slicer 4.4 (http://www.slicer.org). The ILF was selected in each hemisphere according to previous methods, with fronto-occipital and interhemispheric fibers excluded (Wakana *et al.*, 2007). Laterality indices of the ILF were then calculated in terms of tract volume, number of streamlines and fractional anisotropy, as has been done previously (Thiebaut de Schotten *et al.*, 2011). For each value (X), a laterality index was calculated as follows: $(X_{right} - X_{left})/(X_{right} + X_{left})$.

Using DTI, we additionally investigated whether the patient's lesion disrupted connectivity between hemispheres. According to the Witelson classification system (Witelson, 1989; Hofer and Frahm, 2006), the corpus callosum was subdivided into five midsagittal segments: (i) anterior third, (ii) anterior midbody, (iii) posterior midbody, (iv) isthmus and (v) splenium (Supplementary Figure S4). The mean fractional anisotropy of each segment was then measured using 3D Slicer.

The patient provided informed consent for study participation in accord with Partners Institutional Review Board guidelines.

Results

The lesion overlap analysis revealed a region of maximum overlap in the posterior white matter of the right hemisphere, adjacent to the occipital horn of the right lateral ventricle. The majority of the maximum overlap—84%—fell within the right ILF (Figure 3; Supplementary Figure S5). A comparatively small region of the maximum overlap extended to the extrastriate visual cortex (Brodmann area 19). A second, blinded evaluator independently replicated the results, finding a maximum overlap restricted to the same two axial slices as the original analysis ($Z = 0$ and 2), and falling mostly within the right ILF (65% overlap) (Supplementary Figure S6).

In the present patient, structural integrity of the right ILF (in the lesioned hemisphere) appeared diminished compared to the left ILF on DTI (Figure 4). All laterality indices of the ILF were strongly left-lateralized: laterality index of tract volume was −0.74 (8.31 cc on left, 1.25 cc on right), laterality index of streamlines was −0.96 (230 streamlines on left, five streamlines on right) and laterality index of fractional anisotropy was −0.21 (fractional anisotropy of 0.46 on left, 0.30 on right). Of note, healthy individuals, in contrast, have been reported to exhibit no laterality of the ILF in terms of volume or streamlines, and only a slight left-laterality in terms of fractional anisotropy (laterality index of approximately −0.025, a tenth of that in the present patient; Thiebaut de Schotten *et al.*, 2011).

The mean fractional anisotropy in the isthmus (0.45) was markedly lower than in the other four regions of the corpus callosum (0.63 in the anterior third, 0.70 in the anterior midbody, 0.63 in the posterior midbody and 0.73 in the splenium). This drop in fractional anisotropy in the isthmus relative to the other segments of the corpus callosum has not been observed in healthy individuals (Hasan *et al.*, 2008).

Discussion

We present a case of visual hypoemotionality (vision-specific derealization) following a right temporo-parieto-occipital hemorrhage, using a lesion overlap analysis and single-subject DTI to implicate the ILF in the pathophysiology of this condition. Our overlap analysis suggests that lesions associated with visual hypoemotionality all involve the region of the right ILF. We also observed compromised integrity of the right ILF and posterior corpus callosum using DTI tractography.

Bauer, the first to report a case of visual hypoemotionality, hypothesized that injury to the ILF caused a medial temporo-occipital disconnection resulting in a visual-limbic dissociation (Bauer, 1982). His hypothesis was supported by research in animal models (Ross, 2008): in monkeys, bilaterally transecting the longitudinal tracts between the occipital and temporal lobes diminishes their emotional responses to visual stimuli (Horel and Keating, 1972; Horel and Misantone, 1974). Although healthy monkeys will appropriately avoid threatening stimuli based on visual cues alone, monkeys with these temporo-occipital disconnections must first explore stimuli using touch or taste before responding appropriately, despite grossly intact vision.

Our results offer human data to support Bauer's initial hypothesis. It is likely that the right ILF mediates communication between visual and limbic regions (e.g. the amygdala), allowing the emotional processing of visual information. Injury to the ILF may interrupt this transmission, depriving visual experiences of emotional qualities and producing the visual hypoemotionality (or de-affectualization) that commonly underlies experiences of derealization. Dysfunction of this visual-emotional integrative mechanism may occur in non-lesional forms of dissociation as well, potentially explaining why individuals with dissociative experiences exhibit a diminished autonomic response and diminished temporo-occipital activity while viewing emotional images (Phillips *et al.*, 2001; Sierra *et al.*, 2002), and why hypoperfusion of the right medial temporal lobe has been observed in visual hypoemotionality caused by drug toxicity

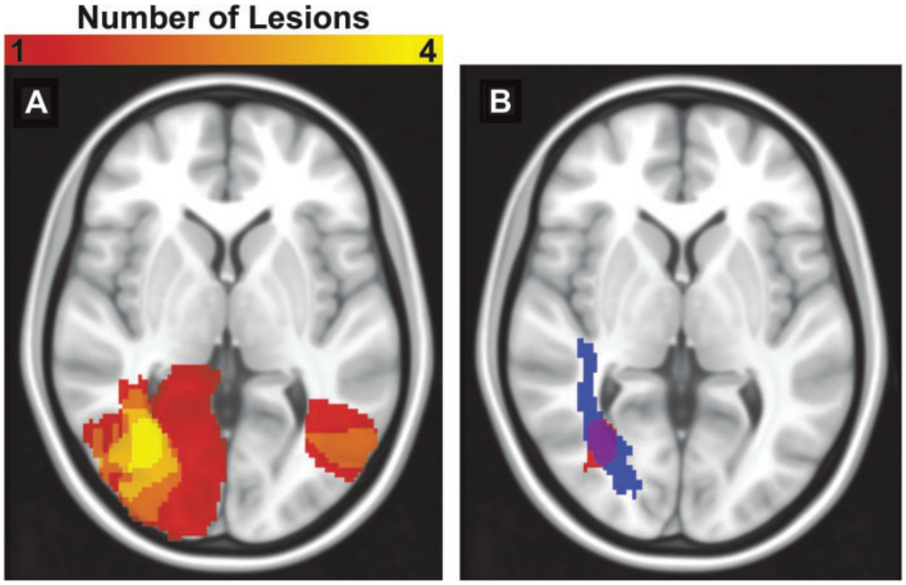

Fig. 3. Normalized lesions were overlapped from all four cases of lesional visual hypoemotionality. (A) Lighter shades of orange represent greater degree of overlap. All four lesions overlap in the posterior white matter of the right hemisphere. (B) The maximum overlap (red) fell over the right inferior longitudinal fasciculus (in blue).

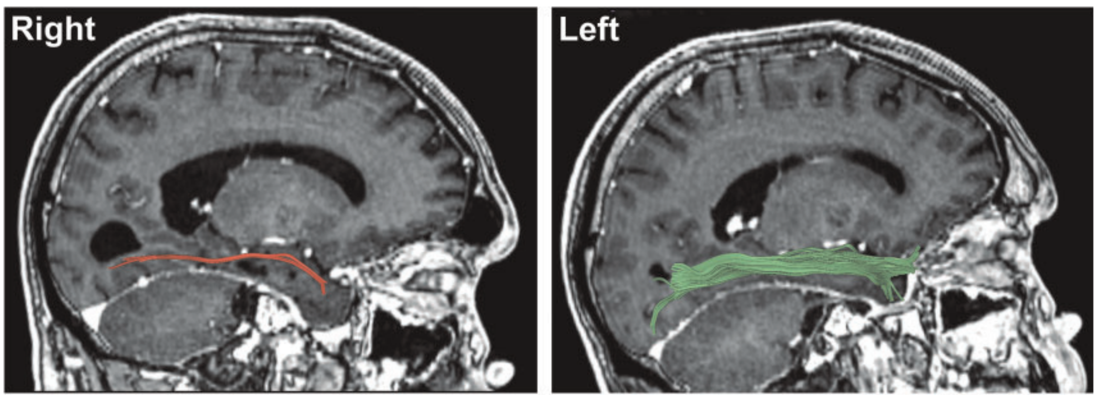

Fig. 4. Diffusion tensor imaging showed diminished structural integrity of the inferior longitudinal fasciculus in the right (lesioned) hemisphere, as compared to the left hemisphere.

(Marianetti *et al.*, 2011). Impairment of this emotional integration mechanism may also account for associations between dissociative experiences and alexithymia (Lemche *et al.*, 2013).

Implication of the ILF in visual-emotional integration may additionally help to explain aspects of similar phenomena such as the Capgras delusion, the belief that an individual one sees has been replaced by an identical imposter (Devinsky, 2009). Like visual hypoemotionality, Capgras delusions have been framed in part as an impairment in the emotional processing of visual information, given that they are often visually specific; affected individuals often believe that only those seen are imposters, while those heard are not (Young *et al.*, 1993). Moreover, patients with Capgras delusion similarly exhibit impairments in face recognition (Young *et al.*, 1993) and have concomitant dissociative experiences (Christodoulou, 1986; Lambert *et al.*, 2002). A similar mechanism of right-lateralized, visual-limbic disconnection has been suggested in this phenomenon (Ellis, 1994; Sierra and Berrios, 1998; Devinsky, 2009). It is therefore possible that the Capgras delusion and visual hypoemotionality share elements of an overlapping pathophysiology.

Our lesion overlap and DTI analyses also add to the literature by indicating that the neural circuits responsible for visual hypoemotionality, and other aspects of visual-emotional integration, are right lateralized. The observation that all four patients exhibited left visual field deficits and some degree of prosopagnosia (which is commonly associated with right-sided lesions; De Renzi *et al.*, 1994), highlights that even in the two cases of bilateral lesions, the right hemisphere was predominantly impaired. The localization of visual-emotional integration to the right hemisphere is also supported by existing research. Patients with right-sided lesions demonstrate impairment in visual identification of emotional stimuli compared to those with left-sided lesions (Borod *et al.*, 1998), and emotionally salient stimuli are processed more rapidly when presented to the left visual field or right hemisphere (Burton and Levy, 1989). Functional MRI studies have also implicated the right temporal cortex in emotional processing (Narumoto *et al.*, 2001; Wager *et al.*, 2003). The right hemisphere is considered dominant in other functions relevant for integrative perceptual processing, including self-recognition, familiarity detection, and self-other boundary evaluations (Devinsky, 2000, 2009).

Although all four lesions studied here directly involved the right ILF, thereby disrupting communication between the right visual cortex and right temporal lobe, it is worth considering whether these lesions also disrupted inter-hemispheric transfer of visual information from the left hemisphere. Two of the previously reported cases involved bilateral lesions of the temporo-occipital region, which were likely sufficient to disrupt projections from bilateral visual cortex (Bauer, 1982; Lopera and Ardila, 1992). The third previously reported case, though only right-sided, was speculated to be large enough to destroy 'the callosal radiations… preventing all commissural transfer of visual information from the left occipital lobe to the right temporal lobe' (Habib, 1986). Our results support and refine the hypothesis that unilateral lesions that cause visual hypoemotionality likely also disrupt inter-hemispheric information transfer, as we show selectively diminished integrity of the posterior aspect of the corpus callosum, and of the isthmus in particular. This finding is supported by studies in monkeys: after destroying the visual cortex in one hemisphere and the temporal lobe in the opposite hemisphere, severing the posterior corpus callosum produces visual hypoemotionality (Horel and Keating, 1969).

Though our results primarily implicate right ILF disruption in visual hypoemotionality, direct injury to visual or limbic regions may additionally contribute to this syndrome. Indeed, while the maximum lesion overlap was based largely over the ILF, it extended slightly into a region of the extrastriate visual cortex. Furthermore, visual hypoemotionality is occasionally associated with disruption of limbic regions as well, as the present patient underwent a medial temporal ablation and one of the previously reported cases of visual hypoemotionality also involved medial temporal injury (Lopera and Ardila, 1992).

In conclusion, using a lesion overlap analysis and DTI tractography, we offer evidence that injury of the right ILF is associated with visual hypoemotionality, a rare visual-limbic disconnection syndrome. This association suggests that the ILF mediates communication between visual and limbic regions, permitting the emotional processing of visual information. These findings lend insight into the neurobiology of dissociation, and more broadly, into the mechanisms integrating visual and emotional experiences into a coherent reality.

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Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest. None declared.

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