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## NEUROANATOMIC CORRELATES OF VISUAL HALLUCINATIONS IN POST-STROKE HEMIANOPIC PATIENTS

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### **ABSTRACT**

Homonymous hemianopia (HH) is the most frequent visual-field defect after a stroke. Some of these patients also suffer from visual hallucinations which origin and frequency remain largely unknown.

**Objectives:** (1) Determine the occurrence of visual hallucinations among post-stroke hemianopic patients in function of the location (Brodmann areas) of the brain lesion, as determined by MRI. (2) Study the neuroanatomic correlates of these hallucinations by nature, frequency and type.

**Methods:** 116 HH patients that had suffered a stroke in the posterior region, including the occipital lobe participated in the study. We evaluated the frequency and nature of visual hallucinations with the Q3H questionnaire. The volume of each patient's brain lesion was modeled in 3D.

**Results:** Of 116 patients with a homonymous hemianopia from a cortical infarction, 85 were excluded due to confounding factors associated with hallucinations. In the final cohort of 31 patients, matched for lesion location and etiology, 58% had experienced hallucinations. A significant inverse correlation between lesion size and the frequency of visual hallucinations emerged. The presence of visual hallucinations in post-stroke hemianopic patients requires a relatively small lesion that includes, at the very least, loss of the striate cortex, but that spares BA19, BA20 and BA37.

**Conclusion:** Our results suggest that visual hallucinations might be due to complex interactions between damaged areas and intact areas of the visual cortex. We discuss these findings regarding models of perception and of visual recognition. Our results also have implications for clinical care of HH patients that have suffered a stroke.

## INTRODUCTION

Homonymous hemianopia (HH) is the most frequent clinical manifestation of visual-field defects following a retrochiasmatic lesion.<sup>1-2</sup> Apart from implicit visual capabilities defined as *blindsight*<sup>3,4</sup>, hemianopic patients can also experience simple or complex visual hallucinations in their blind contralesional visual field<sup>5,6</sup> typically defined as the perception of objects or scenes in the absence of external stimuli<sup>7,8</sup>. They can accompany diverse psychiatric and neurologic pathologies<sup>9,10</sup> as well as ophthalmologic disorders. Charles Bonnet Syndrome (CBS) is thus defined as an association between a decrease in visual acuity and the onset of visual hallucinations.<sup>11</sup> However, hemianopic patients are sometimes mixed in with patients suffering from ophthalmologic deficits and CBS.<sup>12, 13,14</sup>

Visual hallucinations have been mostly reported in patients with cortical blindness<sup>15</sup>, occasionally in hemianopia<sup>16</sup> and in epileptic patients.<sup>17, 18</sup> Winton-Brown et al.<sup>19</sup> proposed that visual hallucinations occur either by deafferentation in the retino-geniculo-striate pathway<sup>20,21</sup> or by suppression of regulatory inhibition in the ascending pathways<sup>22</sup> or finally through a defect in the thalamo-cortical loops.<sup>23</sup> According to neuroimaging studies<sup>24,25</sup>, complex visual hallucinations (faces and objects) are associated to heightened activity in the occipital cortex suggesting that they can be caused by a lesion of the occipital and parietal lobes.<sup>15,26</sup>

Visual hallucinations in hemianopic patients have been reported mostly in case studies<sup>5, 12,18,27-34</sup>, which unfortunately do not enable assessment of their frequency or neuroanatomic bases.

Our objective was to assess the neuroanatomic bases of visual hallucinations in a cohort of post-stroke hemianopic patients, in function of lesion side and location (i.e. Brodmann area).

## MATERIALS & METHODS

### 1. Participants

One-hundred-and-sixteen post-stroke HH patients whose stroke involved the posterior cerebral artery were originally considered for inclusion in the study. The patients ranged in age from 21 years to 92 years old (mean: 58.19 years  $\pm$  16.97 years) and were divided equally by lesion side (58 left HH and 58 right HH). Using the Q3H questionnaire (Questionnaire for Hallucinations in Homonymous Hemianopia)<sup>35</sup> specifically designed to ascertain the frequency and nature of visual hallucinations, we interviewed these patients to assess their possible experiences with visual hallucinations.<sup>6</sup> Among the 116 patients, 48 had experienced visual hallucinations (26 left HH and 22 right HH) and 68 had not (32 left HH and 36 right HH). However, to obtain a homogenous study cohort from the initial one of 116 patients, we excluded those patients (n=85) that had diencephalic or frontal lesions as these had already been shown to be sufficient to cause visual hallucinations<sup>31-34,36</sup> as well as those who underwent medical treatment or had already presented with positive visual phenomena before the stroke. Application of these exclusion criteria to the initial cohort of 116 patients yielded a final cohort of 31 patients (11 women; 35%), ranging in age from 24 years to 88 years old (mean: 57.03 years  $\pm$  17.80 years), all of whom had exhibited HH following a unilateral stroke affecting the occipital lobe (28 ischemic strokes and 3 hemorrhagic strokes) and all of whom were right-handed. These 31 patients were divided into two groups: those who experienced visual hallucinations (n = 18; 8 right HH and 10 left HH) and those who did not (n = 13; 5 right HH and 8 left HH). Each patient's HH was evaluated by visual-field testing (Figure 1 A), either automated (Humphrey) or manual (Goldmann). All patients had normal visual acuity (corrected or uncorrected), did not exhibit any neuropsychological impairments and had not previously experienced any neurologic or troubles, other than their stroke. Relevant to the present study, no patient in the experimental group presented any sign of

psychiatric disorder or delirium. This research was approved by the local ethical committee and patients gave their consent to participate in the study.

For lesion reconstruction, MRI images were acquired on a Philips 3 Tesla unit, in the 3D FLAIR (Fluid-Attenuated Inversion Recovery) 8000 sequence (*Time to repetition*: 8000 ms; *Echo time*: 365 ms; *Matrix size*: 240 x 243 pixels; *Reconstruction size*: 240 x 243 pixels; *Field of view*: 240 x 240 mm; *Flip angle*: 90°; *Voxel size range*: from 0.9 mm to 1.25 mm). Anatomic slices (Figure 1B) were recovered in DICOM format for subsequent 3D visualization using OsiriX Medical Imaging software (OsiriX MD, Pixmeo, Genava, Switzerland). The lesion contours were manually delineated in each 2D slice, thereby enabling reconstruction of a volume of interest (VOI; in cm<sup>3</sup>). To determine the anatomic extent of the lesions, each damaged Brodmann area was individually identified with the help of Brain Voyager software (Brain Innovation, Maastricht, The Netherlands) and checked by a neuroradiologist.

*/Insert Figure 1/*

## 2. Q3H (Questionnaire for **H**allucinations in **H**omonymous **H**emianopia<sup>6, 35</sup>

Visual hallucinations in hemianopic patients have not been systematically researched perhaps, in part, because there is a lack of specific and standardized questionnaire that could be easily used by practitioners. Recognizing this need, our group has developed such a questionnaire for hemianopic patients and more generally, for patients with cortical visual impairment, which was named the *Questionnaire for Hallucinations in Homonymous Hemianopia Patients* (abbreviated as the "Q3H" questionnaire)<sup>35</sup>. For a given patient, this questionnaire enables characterization of their hallucinations (*i.e.* type, frequency, etc.), including determining the extent to which they are aware of the phenomenon.

## 3. Data Analysis

Difference between groups was assessed using Mann–Whitney U test. The degree of association between visual hallucinations (presence/absence) and lesions in Brodmann areas (extent of lesions or presence/absence) was measured with the point biserial and phi coefficients.

*Data statement availability:* The present behavioural and neuroimaging data are available.

## **RESULTS**

### **1 Questionnaire for Hallucinations in Homonymous Hemianopia (Q3H)**

Only one of the 18 patients with hallucinations reported a hallucinatory episode; for all other patients, hallucinations were perceived several times at different times. For 67% of patients, hallucinations were often or very often perceived. Hallucinations lasted from a few seconds to a few minutes in 50% of patients, while they lasted more than 5 minutes in 11% of patients and were perceived continuously in 39% of patients. With respect to critical judgment, 33% of hemianoptic patients believed that their hallucinations were true perceptions, while 67% could criticize them. For all hemianoptic patients (100%), visual hallucinations have always appeared in the blind controlesional visual field, with no temporal regularity. For 78% of patients, visual hallucinations were simple perceptions (lights) while they were complex for 22% of patients (objects, shapes, people). 67% of patients reported hallucinations that were always the same, while 28% of patients reported the same forms with some variations. In only 6% of cases, the hallucinations varied over time. For 94% of patients, hallucinations were grey (like shadows) and colored for only 6% of patients. For 92% of patients, movement was associated with hallucination, while it was a static perception for 18% of patients. For most patients (67%), hallucinations were considered neutral or pleasant, while in 33% of cases, they were perceived as frightening. Finally, for 22% of patients, there were strong similarities between hallucination and a dream, and for 39% of patients these perceptions were quite similar to mental imagery.

A correlation between the items was performed and showed that the frequency of visual hallucinations is positively correlated with their duration ( $r_{sp}=0.63$ ;  $p < .01$ ). Considering the responses to Q3H by lesion side, patients with right HH (left brain-damaged patients) reported greater variability in their hallucinations ( $U = 18$ ,  $p < 0.05$ ) and less similarity to a real visual experience ( $U=63$ ;  $p < 0.05$ ) than patients with left HH (right brain-damaged).

### **Neuro-anatomical correlates of visual hallucinations in hemianopic patients**

Neuroanatomic analysis of the lesions in the study cohort of 31 patients revealed a significant inverse correlation between lesion size and the occurrence of visual hallucinations ( $r_{pb} = 0.47$ ;  $p < 0.1$ ). Thus, the mean lesion volume was significantly smaller ( $U=54$ ;  $p < .05$ ) among the eighteen patients that experienced visual hallucinations ( $Mdn= 9.46$ ;  $m = 14.11 \text{ cm}^3$ ,  $sd = 12.59 \text{ cm}^3$ ) than among the thirteen patients that had not experienced hallucinations ( $Mdn= 27.93$ ;  $m=37.02 \text{ cm}^3$ ;  $sd = 30.34 \text{ cm}^3$ ).

*/Insert Figure 2/*

#### *1.1. Visual hallucinations: relationship to damage in Brodmann areas (BA)*

The occurrence of visual hallucinations was significantly linked to the presence or absence of damage in specific Brodmann areas. For example, in all eighteen (100%) of the patients that had experienced hallucinations, BA20 was spared ( $p = 0.023$ ;  $\phi = -0.453$ ); and in sixteen (89%) of these patients, BA37 was spared ( $p = 0.002$ ;  $\phi = -0.599$ ). Contrariwise, in all of the thirteen patients that did not experience hallucinations (100%), BA19 was damaged ( $p = 0.003$ ;  $\phi = -0.544$ ) (Figure 2).

*/Insert Figure 3/*

Among the eighteen patients that had experienced visual hallucinations, all (100%) of them had suffered an occipital lesion and nine (50%) of them exhibited the same exact lesion profile, in which BA17 and BA18 were both damaged but BA19, BA20 and BA37-39 were all spared. Likewise, the second most frequent lesion profile among these patients, found in six (33%) of them, was that of damage to BA17-19. Interestingly, among the patients that had not experienced hallucinations, six (46%) had a lesion encompassing BA17-19 and BA37. Finally, the presence of a temporal lesion correlated significantly to the absence of visual hallucinations ( $p < 0.001$ ;  $\phi = -0.87$ ). In other words, it seems that for visual hallucinations to occur, the temporal lobe must remain intact. Indeed, sixteen (89%) of the patients that experienced hallucinations did not have a temporal lesion, whereas all (100%) of the thirteen patients that did not experience hallucinations did have a temporal lesion (BA 20, BA 37 or BA 38).

Unfortunately, as presented in Table 1, only two patients with visual hallucinations were proposed an EEG. However, interestingly, in these two patients, the EEG recording was perfectly normal.

## **DISCUSSION**

Previous groups reported only a minor occurrence of visual hallucinations among HH patients, ranging from 2.4%<sup>30</sup> to 15%<sup>26</sup>. In contrast to those findings, in the present study we found that 41% of our initially considered study population of post-stroke HH patients and 58% of our study cohort had experienced hallucinations. The incongruence between previous findings and our own is most likely due to the strict inclusion and exclusion criteria that we used, especially in terms of lesion location and etiology, as well as to the specificity of the Q3H questionnaire. In a study on patients with visual defects unrelated to any ocular pathology, Menon et al.<sup>37</sup> affirmed that 63%

of patients that had been asked about visual hallucinations reported having experienced them, whereas none of them had spontaneously admitted to having experienced hallucinations and only 7% of them alluded to hallucinations on an indirect questionnaire. Crucially, the occurrence of visual hallucinations among HH patients can frequently be underestimated due to the anxiety that they cause patients: not only due to the social stigmas attached to hallucinations, but also because patients may simply be unaware that perceptions in their blind visual field are actually hallucinatory. Indeed, patients often consider perceptions in their contralesional visual field to be a sign of restoration of their visual function. Accordingly, only when using another sensory function (e.g. touch) to assess the perception, do they realize that they are actually hallucinating. The difficulty with which patients become cognizant of their hallucinations most certainly explains why so few patients complain about this issue and why so few clinicians seem interested in it.

*Neuroanatomic correlates and neurophysiologic mechanisms underlying visual hallucinations in hemianopic patients*

Neuroanatomic analysis revealed a significant inverse correlation between lesion size and the occurrence of visual hallucinations. As a matter of fact, based on a highly accurate lesion study, our results suggest that the occurrence of visual hallucinations in post-stroke hemianopic patients requires a relatively small lesion that includes, at the very least, loss of the striate cortex, but that spares BA19, B20 and B37. Nevertheless, although the question of lesion volume has been addressed in previous studies<sup>17</sup>, to date, researchers had attributed the occurrence of visual hallucinations to the presence of the lesion but had scarcely studied the potential influence of damage to specific brain areas. Given that BA19, BA20 and BA37, which are located at the beginning of the ventral pathway, are directly connected to the primary visual cortex and to the

temporal lobe, and consequently, to construction of perception of place<sup>38</sup>, the idea that they are required for occurrence of visual hallucinations makes sense.

Our results confirm the findings of earlier case studies that reported visual hallucinations among hemianopic patients who had suffered lesions that were either limited to the occipital lobe<sup>27-34</sup> or that affected the occipito-parietal lobe.<sup>26,39,40</sup> Moreover, the present findings are further corroborated by several f-MRI studies that revealed activation of the occipital and temporal cortices during visual hallucinations.<sup>25,41</sup> The mechanisms underlying the origin of visual hallucinations among hemianopic patients may be linked to perturbation of cortico-thalamic projections after an occipital lesion, as well as to activation of the adjacent visual association cortex, which would generate percepts.<sup>42</sup> Visual hallucinations would then result from deafferentation due to a loss of cortico-cortical input between the damaged striate cortex and the spared areas of the ventral pathway. The occurrence of visual hallucinations suggests pathologic activation of the feedback signaling from the associated visual areas adjacent to the damaged striate cortex<sup>31,33</sup>, where the neurons, once deprived of their cortical afferent signals, would be more likely to spontaneously fire.<sup>40</sup>

Studies on visual hallucinations in hemianopic patients should be based on a larger patient cohort and should incorporate functional neuroimaging to enable better identification of the underlying neuroanatomy and neurophysiologic mechanisms. We should also improve our understanding of the mechanisms that underpin visual hallucinations in HH to enable improved clinical care of these patients.

## Appendix 1 : Authors

<b>Name</b>	<b>Location</b>	<b>Role</b>	<b>Contribution</b>
Fiora Martinelli Msc Neuropsychology	Fondation Ophtalmologique Rothschild, Paris	Author	Major role in the acquisition and interpretation of data. Drafted and revised the manuscript for intellectual content
Céline Perez PhD	Fondation Ophtalmologique Rothschild, Paris	Author	Major role in recruitment of patients and acquisition of data
Florent Caetta PhD	Fondation Ophtalmologique Rothschild, Paris	Author	Major role in the statistical analysis and interpretation of the data.
Michaël Obadia MD	Fondation Ophtalmologique Rothschild, Paris	Author	Major role in recruitment of patients and acquisition of data
Julien Savatovsky MD	Fondation Ophtalmologique Rothschild, Paris	Author	Major role in recruitment of patients and acquisition of data
Sylvie Chokron, PhD	Fondation Ophtalmologique Rothschild, Paris & CNRS	Author, Chair	Design and conceptualized study; Data interpretation, drafted and revised the manuscript for intellectual content

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## **Figures Legend**

### **Figure 1 :** Visual-field plot and stroke lesions for four patients

(A) Visual-field test revealing HH of four patients from the study cohort.

(B) MRI images (3D FLAIR 8000 sequence), showing the location of the post-stroke lesion in these four patients. The two patients on the left had experienced visual hallucinations, whereas the two patients on the right had not.

### **Figure 2 :** Brodmann area damage and visual hallucinations

### **Figure 3 :** Lesion reconstruction in patients with (3A) or without (3B) visual hallucinations

***Annex 1. Summary of patient data***

<b><i>Visual hallucinations</i></b>	<b><i>Sex</i></b>	<b><i>Age (yrs.)</i></b>	<b><i>Lesion side</i></b>	<b><i>Visual cortex amputation</i></b>	<b><i>Brodmann areas damage</i></b>	<b><i>Lesion volume (cm<sup>3</sup>)</i></b>	<b><i>Hallucination type</i></b>	<b><i>EEG</i></b>
YES	M	68.6	Right	Left HQ	17, 18	37.06	simple	
YES	F	68.6	Right	Left HH	17,18	13.58	simple	
YES	F	41.2	Right	Left HQ	17, 18, 19	6.91	simple	No anomaly
YES	M	63.7	Right	Left HH	17, 18, 19	5.06	complex	
YES	M	58.5	Right	Left HH	17, 18, 19, 37	52.83	complex	
YES	M	26.3	Right	Left HH	17, 18	12.72	simple	-
YES	M	65.9	Right	Left HH	17, 18	15.36	complex	-
YES	M	30.9	Right	Left HQ	17, 18, 19	7.62	simple	-
YES	F	73.5	Right	Left HQ	17, 18, 19	6.40	complex	No anomaly
YES	M	34.5	Right	Left HH	17,18	10.92	simple	-
YES	M	40.2	Left	Right HQ	19, 37	3.42	simple	-
YES	F	29.2	Left	Right HH	18,19	7.23	simple	-
YES	F	76.6	Left	Right HQ	17, 18, 19	19.53	simple	-
YES	M	66.8	Left	Right HH	17,18	8.00	simple	-
YES	M	55.8	Left	Right HH	17, 18	4.98	simple	-
YES	F	66.7	Left	Right HH	17, 18	12.15	simple	-
YES	M	50.1	Left	Right HH	17, 18, 19	22.18	simple	-
YES	M	66.8	Left	Right HH	17,18	8.00	simple	-
NO	M	40	Left	Right HH	17, 19, 20, 37	21.15	-	-
NO	M	75	Left	Right HH	17, 18, 19, 37	27.93	-	-
NO	M	88.7	Left	Right HH	17, 18, 19, 37	56.07	-	-
NO	M	52	Left	Right HH	17, 18, 19, 37	35.86	-	-
NO	M	75.9	Left	Right HH	19, 20, 37, 39	52.43	-	-
NO	M	67.8	Right	Left HH	17, 18, 19, 20, 37, 38	59.58	-	-
NO	F	65.5	Right	Left HH	17, 18, 19, 7, 37	13.05	-	-
NO	F	76.7	Right	Left HH	7, 17, 18, 19, 20,	103.41	-	-
NO	F	51.3	Right	Left HH	18, 19, 37	10.26	-	-
NO	F	30.2	Right	Left HH	17, 18, 19, 37	7.00	-	-
NO	F	24	Right	Left HH	17, 18, 19, 37	10.00	-	-
NO	M	71.9	Right	Left HQ	17, 18, 19, 37	9.00	-	-
NO	M	65.1	Right	Left HH	18, 19, 37	75.55	-	-

(**Abbreviations:** HH: homonymous hemianopia; HQ: homonymous quadrantanopia; yrs: years)