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RETINAL GANGLION CELL DYSFUNCTION IS CORRELATED WITH DISTURBED VISUAL COGNITION IN SCHIZOPHRENIA PATIENTS WITH VISUAL HALLUCINATIONS

Florent BERNARDIN ^{1, 2 *}, Thomas SCHWITZER ^{1, 2, 3}, Karine ANGIOI-DUPREZ ⁴, Anne GIERSCHE ², Fabienne LIGIER ^{5, 6}, Stéphanie BOURION-BEDES ^{6, 7}, Claire JANSEN ¹, Raymund SCHWAN ^{1, 2, 3}, Vincent LAPREVOTE ^{1, 2, 3}.

1- Pôle Hospitalo-Universitaire de Psychiatrie d'Adultes et d'Addictologie du Grand Nancy, Centre Psychothérapeutique de Nancy, Laxou, France

2- Université de Strasbourg, INSERM U1114, Pôle de Psychiatrie, Centre Hospitalier Régional Universitaire de Strasbourg, Strasbourg, France. Electronic address : florent.bernardin@cpn-laxou.com

3- Université de Lorraine, Vandœuvre-lès-Nancy, France

4- Service d'Ophthalmologie, CHRU Nancy, Nancy, France

5-Pôle Universitaire de Psychiatrie de l'Enfant et de l'Adolescent, Centre Psychothérapeutique de Nancy, Laxou, France

6-Université de Lorraine, EA 4360 APEMAC, équipe MICS, Vandœuvre-lès-Nancy, France

7-Service Médico Psychologique Régional, Metz, France

***Address for Correspondence:**

Florent Bernardin
CLIP Centre de Liaison et d'Intervention Précoce
Centre Psychothérapeutique de Nancy
1, rue du Dr Archambault
F-54 520 Laxou
France
florent.bernardin@cpn-laxou.com
phone: +33 3 83 26 08 63

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Abstract

Patients with schizophrenia have altered visual cognition and retinal functions. No studies have explored if retinal anomalies are related to visual cognition and the presence of visual hallucinations (VH).

We explored functional responses of the retinal ganglion cells in schizophrenia patients with or without VH and conducted a neuropsychological evaluation to explore the links between cognition and retinal function.

The VH+ group showed poorer visual cognition and we found correlations between the amplitudes of the P50 and the N95 waves and visual cognition.

Our results provide arguments for a link between retinal dysfunction, impaired visual processing and VH in schizophrenia.

Keywords: retinal ganglion cell, visual hallucinations, visual cognition

Introduction

Schizophrenia is characterized by multiple visual processing impairments and retinal dysfunctions of the photoreceptors, bipolar cells and retinal ganglion cells (RGC) (Adams and Nasrallah, 2018). Studying RGC is crucial as they are the last stage of retinal processing and abnormalities of RGC functioning could affect later stages of visual processing (Heravian et al., 2011). Pattern electroretinograms (PERG) are recommended by the International Society for Clinical Electrophysiology of Vision (ISCEV) standards as the most accurate measurement of the RGC (Bach et al., 2013). PERG enables evaluation of two main waves of interest: the P50 wave, which is generated by RGC and partly by bipolar cells, and the N95 wave, which represents RGC activity (Froehlich and Kaufman, 1993) and is its best marker (Bach et al., 2013). We recently reported an increase in N95 implicit time that supports a delay in the emission of action potentials by RGC. Moreover, the subgroup of patients with visual hallucinations (VH) presented a specific alteration of the rod system that can be considered as an aggravating factor for developing VH in schizophrenia patients (Bernardin et al., 2020).

Patients with schizophrenia have impaired visual processing with form and object recognition deficits (Gabrovska et al., 2003; Kimhy et al., 2007). Using the Visual and Object Space Perception battery (VOSP) (James and Warrington, 1991), and Gabrovska et al. (2003), showed that the performance pattern in patients with schizophrenia was similar to visual associative agnosia in neurological disorders. Likewise, the VOSP battery is of interest for VH symptoms as it has been shown to be able to discriminate between patients with and without VH in Parkinson's disease (Barnes et al., 2003). **Despite these studies, little is known about how visual impairments contribute to visual symptoms, such as abnormal perception and visual hallucinations, observed clinically in patients with schizophrenia. Our approach is**

inspired by the results obtained in Parkinson's disease that suggest a link between visual processing and hallucinations (Meppelink et al., 2009). Understanding the possible role of retina dysfunction in VH could also help understand this symptom in schizophrenia, and our findings may be important for the management of visual deficits in schizophrenia. Visual training is promising (Kurylo et al., 2017; Kurylo et al., 2018) but the benefits for visual hallucinations remain to be assessed. This is all the more important as although VH are underestimated in schizophrenia, they are associated with a poorer prognosis (Clark et al., 2017) and a higher risk of mortality (Chouinard et al., 2019).

Although a link between retinal dysfunctions and VH has been explored in schizophrenia (Bernardin et al., 2020) and in Parkinson's disease (Lee et al., 2014), and between visual cognition and VH in Parkinson's disease (Barnes et al., 2003), to date, no study has explored the links between retinal dysfunction, visual cognition and VH in schizophrenia. The aim of the present study was thus to explore these connections to further advance our understanding of visual symptoms in schizophrenia.

Methods

Study population

This study met the requirements of the Declaration of Helsinki (World Medical Association, 2013), was approved by the Nancy University Hospital Ethics Committee (2013-A00097-38 CPP 13.02.02), and was registered with clinicaltrials.gov (identifier: NCT02864680). Twenty-nine patients with schizophrenia were previously recruited for a larger ongoing project, called Causa Map (Schwitzer et al., 2017).

The patients fulfilled the DSM IV-TR Axis I Disorders criteria for schizophrenia. Current (past month) and lifetime visual and auditory hallucinations were assessed using the Psycho-Sensory hAllucination Scale (PSAS). The PSAS provides an index of the gravity of the hallucinations, and represents the sum of scores for the clinical characteristics of hallucinations such as frequency, duration, negative aspects, conviction, impact, control and sound intensity (for auditory hallucinations) (de Chazeron et al., 2015). Patients were subdivided into two subgroups depending on the presence or absence of VH: the VH+ group (N = 12) and the VH- group (N = 17). Three patients had a history of cannabis but the interview allowed us to **clarify** that none of their VH was induced by THC. In addition, the Cannabis Abuse Screening Test (CAST) and the Alcohol Use Disorder Identification Test (AUDIT) were used to assess use, abuse, or dependence on cannabis and/or alcohol. Details of the demographic, clinical, substance use and hallucinations characteristics are given in Table 1. The modalities of recruitment and inclusion criteria of the patients with schizophrenia are described in Bernardin et al. (2019).

Neuropsychological evaluation

For each specific cognitive domain, the French version of the following neuropsychological tests were administered: National Adult Reading Test (Nelson and Willison, 1991); the California Verbal Learning Test (Delis et al., 1988); the verbal fluency test (Roussel and Godefroy, 2008); working memory, Go/No-go and divided attention subtests of the Test of Attentional Performance (Zimmermann and Fimm, 1995); coding subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1997) and the VOSP battery (James & Warrington, 1991). The VOSP battery has two indices: the VOSP-Object index, which groups subtests that evaluate shape and object recognition, and the VOSP-Space index, which groups subtests that evaluate spatial relationships of both 2D and 3D objects.

PERG measurements

The MonPackOne system (Metrovision) was used for stimulation, recording, and analysis of the PERG. Electrical signals were recorded simultaneously for both eyes (averaged for analysis) on non-dilated pupils, with Dawson-Trick-Litzkow (DTL) electrodes placed at the bottom of the conjunctival sac. The ground electrode is attached to the subject's forehead and reference electrode to his/her external canthi. RGC functions were explored using the PERG measurements as recommended in the ISCEV standards (Bach et al., 2013).

Statistical analysis

Statistical analyses were conducted using STATISTICA 10 software (StatSoft Inc.). The differences between the groups were analyzed using a t test for independent samples. The Mann-Whitney U-test was used for scores with non-normal distribution. Correlation analyses

were performed using Spearman's Rank Correlation test. Finally, we conducted a logistic regression to check whether VOSP performances could predict the presence of VH in the history of the disease.

Results

PERG measurements: P50 and N95 amplitudes and implicit times

The Mann-Whitney U test revealed no significant difference between the VH+ and VH- groups in P50 implicit time ($U = 85.0, p = \text{n.s.}$), P50 amplitude ($U = 84.5, p = \text{n.s.}$), N95 implicit time ($U = 74.0, p = \text{ns.}$) and N95 amplitude ($U = 93.0, p = \text{n.s.}$).

Neuropsychological evaluation

Only performances in the VOSP battery revealed significant differences between the VH+ and the VH- groups. The VOSP-object index was significantly lower in the VH+ group ($t(27) = 2.68, p < .05, d = 0.96$) as was the VOSP-space index ($U = 52.0, p < .05, \eta^2 = 0.17$) (Table 1).

Spearman's rank-order correlations showed no significant correlation between CAST and AUDIT scores and VOSP performances and between performances in attentional or working memory tests and the VOSP-Object and VOSP-Space indices in either the VH+ or the VH- group.

To determine whether the occurrence of VH in the history of the disease could be predicted by VOSP performances, we performed the logistic regression with the VOSP-object index as a continuous predictor. Results showed that a weak VOSP-object index significantly predicted the presence of VH in the group of patients with schizophrenia ($\chi^2(1) = 6.55, p < .05$, odds ratio = 6.5, 72.4% of the subjects were correctly classified in their respective group: 82.3% for the VH- group and 58.3% for the VH+ group).

[insert Table 1 here]

Visual cognition and RGC functions

In the VH+ group, Spearman's rank-order correlations showed significant correlations between the P50 amplitude and the VOSP-object index ($r = 0.61, p < .05$) and between the N95 amplitude and the VOSP-object index ($r = -0.58, p < .05$).

In the VH- group, no significant correlation was found between RGC parameters and VOSP-object or VOSP-space indices.

Discussion

Our results showed that there was no difference in RGC functions between the VH+ and VH- groups. Nonetheless, regarding visual cognition, the performances of the VOSP-object and the VOSP-space indices were significantly lower in the VH+ group. However, it should be noted that VOSP performances in the VH+ group were not associated with attention or working memory performances. They therefore constituted a genuine deficit in visual cognition independent of attention deficits. Furthermore, the logistic regression showed that the VOSP-object index significantly predicted the risk of VH. Finally, we found significant correlations selectively within the VH+ group between the amplitudes of the P50 and N95 waves of the RGC and the VOSP-object index performances.

Taken together, these results provide arguments for a link between abnormalities of early visual processing, retinal functions, and presence of VH in patients with schizophrenia. The significant association between the functional response of RGC and reduced performances in the VOSP battery allow us to propose the hypothesis that reduced responses of RGC are related to reduced bottom-up visual information processing in patients with VH.

The ability of VOSP and visual tasks close to the VOSP to distinguish between patients with and without VH has been demonstrated in Parkinson's disease (Barnes et al., 2003; Meppelink et al., 2008). Moreover in Parkinson's disease, some authors showed that retinal dysfunctions were linked to visual disturbances (Nowacka et al., 2015) and that altered microstructural integrity of the optic nerve was a predictor of visuospatial cognitive dysfunction (Lee et al., 2016). Meppelink et al. (2009) showed that vulnerability to VHs was associated with impaired visual processing in ventral/lateral visual association cortices in patients with Parkinson's disease and VH, suggesting impaired bottom-up visual processing. Our results suggest similar conclusions as VH are associated with visual cognition deficits in schizophrenia patients with

VH. The Activation Input and Modulation model adapted by Diederich et al. (2005) opens the door for retinal involvement as a contributor to very early deficit input in VH. Combined with our previous results (Bernardin et al., 2020), we show that both RGC and rod dysfunction are directly or indirectly associated with visual impairments and VH in schizophrenia. Our results are also in line with those of previous studies showing that impairment in early stages of sensory processing such as visuo-perceptive processing deficits may lead to perceptual incoherence that ultimately favor positive symptoms such as delusions (Schmack et al., 2015) or hallucinations (Postmes et al., 2014).

In addition to VH symptoms, schizophrenia and Parkinson's disease share common visual disorders that affect contrast sensitivity due to retinal dysfunctions (Cadenhead et al., 2013) and object, visuospatial, or motion perception (Gabrovska et al., 2003; Silverstein and Keane, 2011; Weil et al., 2016). To the best of our knowledge, this is the first report to show that, in schizophrenia, retinal dysfunctions can be linked to both visual cognition and VH. Hence, visual information may already deteriorate at the retinal stage and could contribute to poor bottom-up sensory input and to both altered visual cognition and the emergence of VH (for a review of cognitive models of VH see Bernardin et al., 2017). [It would be of great interest to explore this implication by studying vision in schizophrenia by simultaneously recording both ERG and visual evoked potential measures.](#)

This study had several limitations. First, three patients were regular cannabis consumers (two in the VH- group and one in the VH+ group). In our previous study in this population, we showed that CAST scores did not differ between the VH+ and the VH- groups and were not correlated with RGC measurements (Bernardin et al., 2020). Second, our results are based on correlations obtained with small samples, which weakens the predictive power of our statistical analyses.

To conclude, our results provide arguments for a link between retinal response and visual information processing deficits favoring the emergence of VH in people suffering from schizophrenia with VH.

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Conflicts of interest

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Table 1. Demographic, clinical, substance use characteristics and VOSP scores for the VH+ and VH- groups

	VH+ group N=12	VH- group N=17	<i>p</i>
Sex: men/women (%)	92/8	71/29	n.s. †
Age (years)	30 [24:37]	23 [23:30]	n.s
Education (years)	12.0 [11:13]	12 [12:13]	n.s
AUDIT	0.0 [0.0:4.0]	1.0 [0.0:10.0]	n.s
CAST	0.0 [0.0:5.0]	0.0 [0.0:5.0]	n.s
Disease duration (months)	87.0 [48.7:188.8]	27.0 [21.2:102.9]	n.s
PANSS - Global	63 [52.8:73.9]	64 [56.1:67.9]	n.s
PANSS - Positive	13.5 [11.6:19.2]	13.0 [11.1:14.7]	n.s
PANSS - Negative	16.0 [12.9:19.2]	20.0 [15.0:21.0]	n.s
PANSS - General	30.0 [24.7:36.4]	32.0 [28.3:33.8]	n.s
PSAS LIFETIME:			
N° of subjects with VH	12	0	-
N° of subjects with AH	10	17	-
Lifetime repercussion index (VH)	13.0 [10.2:17.5]	NA	-
Lifetime repercussion index (AH)	19.5 [9.2:20.7]	0.0 [2.9:11.4]	<i>p</i> < .05 ⁺
PSAS CURRENT:			
N° of subjects with VH	2	0	-
N° of subjects with AH	3	1	-
Current repercussion index (VH)	0.0 [-0.8:4.3]	NA	-
Current repercussion index (AH)	0.0 [-0.6:6.8]	0.0 [-0.9:2.6]	n.s
Chlorpromazine equivalent (mean (sd))	437.8 (230.8)	489 (280)	n.s
Diazepam equivalent	0.0 [-0.7:3.8]	0.0 [-3.8:11.7]	n.s
VOSP-object index	84.2 (5.8)	88.8 (3.3)	<i>p</i> < .05 *
Screening	19.5 [18.3:19.9]	20.0 [18.8:20.0]	n.s
Incomplete letters	20.0 [19.2:20.0]	20.0 [19.1:19.9]	n.s
Silhouettes	19.3 (4.4)	21.6 (2.5)	<i>p</i> = .08 *
Object decision	16.4 (2.2)	17.3 (1.8)	n.s
Progressive silhouettes	9.8 (2.5)	11.1 (3.0)	n.s
VOSP-space index	48.0 [45.0:48.9]	49.0 [48.1:49.6]	<i>p</i> < .05 ⁺
Dot counting	9.5 [7.5:10.0]	10.0 [9.6:9.3]	n.s
Position discrimination	20.0 [19.6:20.0]	20.0 [19.9:19.6]	n.s
Number localization	10.0 [8.5:10.0]	10.0 [9.6:9.3]	n.s
Cubes	9.0 [9.3:9.8]	10.0 [9.8:9.5]	<i>p</i> = .09 ⁺
P50 implicit time	52.4 [49.5:54.9]	51.8 [48.9:52.9]	n.s
P50 amplitude	2.6 [2.1:3.1]	2.2 [2.1:3.1]	n.s
N95 implicit time	94.3 [88.7:98.2]	96.5 [93.6:101.0]	n.s
N95 amplitude	-3.3 [-4.3:-2.8]	-3.2 [-4.5:-2.7]	n.s

Data are presented as median [95% CI] and mean (standard deviation) when indicated.

VH+: Schizophrenia patients with visual hallucinations

VH- group: Schizophrenia patients with auditory hallucinations or no hallucinations

AUDIT: Alcohol Use Disorder Identification Test score

CAST: Cannabis Use Screening Test score

PSAS: Psycho-Sensory hAllucination Scale

VOSP: Visual Object Space Perception

† Pearson chi-square

+ Mann-Whitney U test

* t test for independent samples