Occipital cortex and cerebellum grey matter changes in visual snow syndrome

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Statistical and imaging analysis was performed by author FP, with the supervision of authors MB, OOD and DF.

**Abstract**

**Objective:** To determine whether regional grey and white matter differences characterize the brain of patients with visual snow syndrome, a newly defined neurological condition, we used a voxel-based morphometry approach.

**Methods:** In order to investigate directly whole brain morphology, we performed a magnetic resonance imaging study on patients \((n = 24)\) with visual snow syndrome and on age- and gender matched \((n = 24)\) healthy volunteers. Voxel-based morphometry was used to determine volumetric differences in visual snow subjects. We further analysed cerebellar anatomy directly using the high-resolution spatially unbiased atlas template of the cerebellum.

**Results:** Compared to healthy controls, patients with visual snow syndrome had increased grey matter volume in the left primary and secondary visual cortices, the left visual motion area V5 and the left cerebellar crus I/lobule VI area. These anatomical alterations could not be explained by clinical features of the condition.

**Conclusions:** We conclude that patients with visual snow syndrome have subtle, yet significant neuroanatomical differences in key visual and lateral cerebellar areas, which may in part explain the pathophysiological basis of the disorder.
Introduction

Visual snow syndrome (VSS) is a chronic neurological condition in which the chief symptom is a constant perception of small moving dots occupying the entire visual field. Other symptoms include palinopsia, photophobia, entoptic phenomena and nyctalopia, which are experienced in different combinations within the syndrome. Visual snow can vary in severity, and it is most disabling when it is accompanied by comorbidities such as migraine and tinnitus.

The pathophysiology of VSS is largely unknown. By investigating brain metabolism in visual snow patients, an $^{18}$F-FDG PET study revealed significant hypermetabolism in the lingual gyrus as well as a trend of increased metabolism in the left cerebellum.

Gross neuroanatomical abnormalities, as detected by standard clinical neuroimaging, should be excluded for the diagnosis of visual snow, as this is not a ‘secondary’ neurological condition. Nonetheless, it is unclear whether subtle morphological differences might be in part driving, or perhaps be caused by, the disorder.

Using a voxel-based whole-brain morphometry (VBM) approach, we studied the neuroanatomical differences between patients with visual snow syndrome compared to healthy volunteers. We also directly investigated cerebellar anatomy using the high-resolution atlas template SUIT: a spatially unbiased atlas template of the cerebellum and brainstem. We hypothesized that anatomical differences in VSS would involve the visual network, in particular the primary and secondary visual cortices (areas V1/V2), the pre-cortical visual pathways, as well as the visual motion processing area V5 and the cerebellum. Here, areas showing metabolic alterations with $^{18}$F-FDG PET, could potentially present morphological grey and white matter differences in VSS subjects.
Methods

Subject population and recruitment

Twenty-four patients with a diagnosis of visual snow syndrome and an equal number of age and gender-matched healthy volunteers were selected for the study. We recruited patients by email, re-approaching subjects who had previously contacted our study team asking to participate in research studies. Healthy volunteers were recruited through internal advertisement at King’s College London.

Inclusion criteria for participants were: age 20–60 years, no contraindications to MRI, no serious medical conditions including psychiatric comorbidities (as assessed by a trained neurologist), no recurrent use of medications with an action on the central nervous system and no previous use of any recreational drugs. Healthy volunteers were selected based on matching age (± 5 years) and gender of our patient population and had no ongoing medical condition or medication use.

The study involved a telephone interview by a neurologist to assess eligibility of participants, and either one or two visits to our research facility, depending if the subject was in the control or patient group, respectively. A full medical history, general and neurological examinations were performed for each participant.

Standard Protocol Approvals and Patient Consents

All participants gave their informed consent. The study was approved by the London - City & East Research Ethics Committee (Reference number: 16/LO/0964).

Magnetic resonance imaging
MR scanning took place on the second visit for patients and the first for volunteers, and lasted in total approximately 70 minutes. All subjects were scanned between 9 and 12 am and told to consume a light breakfast and to avoid caffeine on the morning of the visit. The scanning protocol was the same for both groups and was conducted over a single session. All scans were performed on a 3T General Electric MR750 MRI scanner at the NIHR-Wellcome Trust King’s Clinical Research Facility, King’s College Hospital, London using a 12-channel head coil. High resolution 3D T1-weighted IR-SPGR images were acquired with the following parameters: TR = 7.312 ms; TE = 3.016 ms; TI = 400 ms; FOV = 270 mm; matrix = 256x256; slice thickness = 1.2 mm; voxel dimension = 1.05mm x 1.05mm x 1.2 mm; 196 slice partitions, ASSET factor = 1.75, in-plane resolution = 1 mm.

**Voxel-based morphometry with DARTEL**

Prior to analysis, raw T1 images were visually inspected for artefacts and structural abnormalities that could interfere with the analysis. None of the acquired images were discarded.

MRI data was processed and analysed using the Statistical Parametric Mapping software suite, version 12 (SPM 12; [www.fil.ion.ucl.ac.uk/spm/](http://www.fil.ion.ucl.ac.uk/spm/)) on a Matlab platform ([MATLAB R2017a](https://uk.mathworks.com/)).

VBM analysis to localize regional differences in grey and white matter volume was first conducted by applying diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) algorithm following the default parameters. This is a well-accepted automated method for VBM, that achieves a more precise registration of individual brain images. In essence, DARTEL allows avoidance of biased image registration by creating an intermediate study-specific template based on the brains of the participants in the study, and by modelling the spatial deformations through a single velocity field that is constant over unit time.
The first step of the procedure segmented each subject’s image into grey matter (GM), white matter (WM), and cerebral spinal fluid (CSF). The second step created a DARTEL population template derived from nonlinear deformation fields for the segmentation procedure and registers all individual deformations to the DARTEL template. In the next registration step, a non-linear warping of the segmented images allowed to register the DARTEL template in Montreal Neurological Institute (MNI) space. Furthermore, the voxel values in the tissue maps were modulated by the Jacobian determinant calculated during spatial normalization. Total intracranial volume (TIV) was calculated for each subject within Matlab from the GM, WM and CSF tissue components. Finally, all modulated and normalized grey and white matter segments were smoothed with full width at half-maximum isotropic Gaussian kernel of 8-mm.

**Structural cerebellar analysis using SUIT**

To analyse regional cerebellar volumes we used the SUIT toolbox version 3.3 ([https://www.fil.ion.ucl.ac.uk/spm/ext/](https://www.fil.ion.ucl.ac.uk/spm/ext/)) within SPM12. This toolbox provides a high-resolution atlas template of the human cerebellum and brainstem that preserves the anatomical detail of cerebellar structures, as well as dedicated procedures to isolate automatically cerebellar structures from the cerebral cortex and to normalise accurately cerebellar structures to this template. Prior to normalisation, the individually created isolation maps were loaded into FSLView ([www.fmrib.ox.ac.uk/fsl/](http://www.fmrib.ox.ac.uk/fsl/)) where they were visually inspected against the cropped image and hand corrected if necessary. Using the inverse of the resulting normalisation transform, a parcellation of the cerebellum was obtained, based on the probabilistic magnetic resonance atlas of the human cerebellum provided within the SUIT toolbox. Volumes of interest were then overlaid onto each individual participant’s structural scan and inspected to ensure accurate registration.
VBM analyses

VBM analyses included whole-brain and parcellated cerebellar GM and WM analyses, as well as region-of-interest (ROI) grey matter analyses.

For the whole-brain voxel-wise analysis, GM and WM volumes between subgroups of VSS patients and controls were reviewed with 2-sample \( t \)-tests at an initial cluster-forming voxel threshold of \( p < 0.001 \). All results were family-wise error (FWE) corrected for multiple comparisons to \( p < 0.05 \) using the Gaussian random field theory on the basis of cluster extent. Total intracranial volume, subject age, gender, handedness and number of disease years were added as covariates in our model. We ran a second model with migraine history as a covariate, since this condition was not present in the control group. An absolute threshold mask of 0.1 was used on both the GM and WM to avoid possible edge effects around the border between the two.

For the cerebellar analysis, morphological group differences in parcellated cerebellar GM and WM volumes were assessed using the general linear model. TIV of each participant was entered into the design matrix as a nuisance covariate. Further analyses covarying for age, gender, handedness, number of disease years and migraine presence were also run. The same voxel-wise significance thresholds and masking as the whole-brain analysis were used.

ROI analyses were carried out in the following visual areas: bilateral primary visual cortex (V1/V2), visual motion processing area V5 and the pulvinar. To create ROIs for these anatomical areas we used the ‘wfu_pickupatlas Anatomical Library’ (https://www.nitrc.org/projects/wfu_pickatlas), as implemented in the SPM toolbox, with the exception of the V5 ROI that was created from the ‘Juelich Histological Atlas’ within FSLeyes. We also defined two a priori ROIs based on coordinates from the previous \(^{18}\text{F}-\text{FDG PET study on visual snow}^4 \). These were namely the right lingual gyrus \((x = 16, y = -78, z = -5)\) and the left cerebellum \((x = -12, y = -62, z = -9)\); the coordinates were used for small volume correction (SVC) with a sphere of radius 10mm. Statistical inferences were made at voxel-wise peak level \( p < 0.05 \)
with family-wise error (FWE) correction for multiple comparisons within all the voxels of the ROI. As the cerebellar volumes from SUIT were already parcellated to a small anatomical region, ROI analyses were not performed on these images.

Descriptive statistics and correlation analyses for this study were performed with SPSS Statistics version 24.0 for Windows (IBM, Armonk, NY: IBM Corp.; http://www.spss.com). Pearson correlation coefficients were used to analyse relationships between continuous variables. \( P < 0.05 \) was considered significant.

**Data Availability**

The data that support the findings of this study are available from the study team upon reasonable request.

**Results**

**Demographic and clinical data**

There were no significant differences with regards to age (mean ± standard deviation for VSS patients 28 ± 6 and controls 28 ± 5; \( p = 0.8 \)), gender (female:male ratio for VSS patients 12:12 and controls 14:10; \( p = 0.6 \)) or handedness (right:left ratio for VSS patients 21:3 and controls 23:1; \( p = 0.3 \)) among the two groups. Demographic characteristics and clinical features of the VSS group are summarized in Table 1, along with a list of concomitant medication at the time of the study and presence of migraine comorbidity.

**Whole-brain VBM-DARTEL analysis**

VSS patients showed no differences in average total intracranial volume with respect to controls (1465 ± 113 ml vs. 1450 ± 146 ml; \( p = 0.6 \)).
A whole-brain voxel-wise GM analysis revealed a cluster of increased grey matter in VSS patients with respect to controls in the left primary visual cortex (x = -2, y = -98, z = 3; k = 594; \( p = 0.007 \) uncorrected, \( p = 0.06 \) FWE corrected; Figure 1). When the cluster forming threshold was reduced to \( p = 0.005 \), this area was significant (\( p = 0.02 \) FWE corrected). Further, when lowering the threshold to \( p = 0.01 \) for exploratory purposes, the significant cluster appeared to extend to the homologous region of the contralateral side as well.

No significant differences in white matter volumes were found between the two groups.

**ROI analysis of GM volumes**

Our ROI analyses showed a significant GM volume difference in the left V1/V2 area (main cluster: x = -3, y = -94, z = 0; k = 22; \( p = 0.04 \) FWE) analogous to the cluster from the whole-brain analysis, as well as in the left V5 area (x = -38, y = -75, z = 4; k = 32; \( p = 0.04 \) FWE) in VSS. When covarying for migraine presence, both of these areas survived significance.

No significant GM volume differences were found for the remaining regions of interest.

**Cerebellar analysis with SUIT**

Cerebellar images for one control subject had to be discarded due to poor image quality.

While the whole-brain VBM analysis did not reveal any specific morphological differences in the cerebellum of VS patients, when analysing the parcellated volumes created with SUIT and corrected by total intracranial volume, we found an area of significant increase of grey matter volume in crus I/lobule VI of the left cerebellar hemisphere (x = -12, y = -62, z = -23; k = 25; \( p = 0.02 \) FWE; Figure 2). When correcting for age, gender, handedness, migraine and duration of disease, this area was not significant. However, upon removing one variable at a time from our
model we were able to determine that the area of increased GM was present when we co-varied for age and handedness and was significant at a reduced statistical threshold of $p = 0.005$ for the covariates of gender and presence of migraine; finally, it was not significant even at reduced thresholds for the covariate number of disease years. To characterize this further, we examined the beta values for the cluster and ran a multiple regression analysis in SPM on VS subjects only, finding no significant relationship between the increase in grey matter volume and number of years with the disease.

We found no significant WM volume differences or GM volume decreases in the cerebellum in patients with VSS respect to healthy controls.

A summary of all significant areas of grey matter volume increase in patients with VSS can be found in Table 2 and Figure 3.

**Correlations with clinical features**

We extracted the contrast tissue volume estimate values from the left V1, left V5 and cerebellar *a priori* defined ROIs in all participants and correlated these values with the following variables: age, gender, handedness (in both groups), migraine presence, sum of associated visual symptoms and disease years (in patients only). No significant correlation was found.
Discussion

The main finding of our study was that patients with visual snow syndrome exhibit morphological changes in grey matter volume of the left occipital cortex and cerebellum when compared with matched controls. Overall, the results seem to confirm the presence of central nervous system changes in VSS, underscoring the fundamentally biological basis of the problem. Given that the anatomical changes were not associated with clinical features, such as the total number of disease years and an index of VSS severity, we suggest that they may represent an inherent trait of visual snow, rather than a consequence of the condition.

The morphological differences emerging from our analysis involving the primary visual cortex (Figure 1) and the visual motion network are in line with the perception of a moving, pan-field visual illusion in VSS. These areas also emerged from our whole-brain analyses, confirming their importance in this neurological syndrome, and configuring it as a disorder of complex visual processing.

The further involvement of cerebellar areas widely connected with frontal neocortical regions (Figure 2), suggests that aside from a sensory dysfunction of visual perception, VSS could also represent a broader network-type disorder, in which more complex alterations of cognitive processing and integration of internal and external stimuli are at play. The analyses including clinical covariates of interest showed that duration of disease in years was the only variable for which this cerebellar area was completely absent, possibly because of some degree of shared variance between the covariate and the increased grey matter volume, which might have rendered the result non-significant. Nonetheless, it must be noted that this effect was not explained by the duration of disease itself. Further, the reliability of number of years with the condition could be susceptible to recall biases, possibly hindering its validity as a clinical measure.
In patients with VSS, there were no significant structural differences in the lingual gyrus, where metabolic alterations were previously found with $[^{18}\text{F}]-\text{FDG PET}$.

*Primary visual cortex involvement*

Considering that visual snow syndrome is a disorder linked to alterations in brain function, the absence of major changes in morphology was expected. Conversely, an altered structure of primary and secondary visual areas is in keeping with the clinical experience of simple visual illusions typical of visual snow. Furthermore, GM increases in the primary visual cortex very clearly followed the calcarine fissure (Figure 1), showing a correspondence to the retinotopic mapping of the entire hemi-field.

The fact that the morphological V1 change was only found in the left side is more difficult to interpret. It is possible that this finding was due to a statistical issue, rather than to a truly lateralized morphological difference, given that a grey matter volume increase was also present in the same region on the right side when lowering the significance threshold. Further, it is unlikely this was due to handedness, as this variable was corrected for in the analysis. Interestingly, we found no morphological alterations of pre-cortical visual pathways in this study.

*Increased GM volume within the visual motion network*

The visual motion network spreads from V1 dorsally to the parietal lobe, encompassing visual motion area V5, which is located in the ventrolateral temporo-parietal-occipital junction and specifically responds to motion stimuli. This area is involved primarily in decoding information and patterns of direction, speed and motion. The motion network is also composed of sub-compartments within V1/V2, of area V3/V3A in the cuneus and finally of Broadmann area 7 in the precuneus. It is part of the dorsal stream, now renamed the ‘how-pathway’, which integrates
information on spatial localisation of incoming visual information for the purpose of skilled motor planning. Importantly, area V5 was also identified in a recent study of regional brain perfusion in visual snow.

Cerebellar alterations in visual snow syndrome

In addition to differences in neocortical visual networks, we also demonstrated differences in the lateral cerebellum in VSS patients when compared with controls. The left cerebellar lobule VI showed increased metabolism in a previous $^{[18]}\text{F}$-FDG PET study, in an area contiguous with the one found in the present study. This constitutes a possible link between the previously documented functional alteration and an underlying structural abnormality in visual snow syndrome. This region is directly involved in spatial processing functions and in the ‘preparation’ of somatosensory integration. Most importantly, the cerebellar lobule VI/Crus I form part of the so-called ‘cognitive cerebellum’, which, thanks to widespread cerebello-cortical connections, has a role in complex functions such as language, executive action and visual working memory. In particular, these cerebellar sub-regions have been associated with the fronto-parietal and default mode networks (DMN) in resting state analyses. These networks are control systems that work in synergy when the brain is involved in a task or at rest. The fronto-parietal network in particular is involved in top-down attentional control and adaptation behaviours, whereas the DMN is responsible for monitoring the internal mental landscape.

A complex dysfunction of visual processing and brain networks in VSS

Several pathophysiological hypotheses for the genesis of VSS have been proposed in the literature, and hyperexcitation of primary and secondary visual cortices seems to be one of the most plausible. In a condition where internal visual information is constantly being perceived, a state of
increased cortical activation, justified by a form of processing overload, is certainly plausible. We hypothesize that this functional hyperactivation could in turn be causing localised increases in grey matter volume, such as the ones we found in our study. Interestingly, important pathways involved in integration and processing of visual stimuli as well as action and attention networks were simultaneously affected in visual snow syndrome, an aspect that will need to be explored in future studies.

Migraine comorbidity and VSS

A similar disorder of brain function that has been linked to visual snow, both on a clinical and pathophysiological basis, is migraine. The high comorbidity between these conditions was confirmed in our population, where more than half the subjects presented a history of migraine.

Several studies have shown morphological grey and white matter changes in the visual areas and cerebellum of migraineurs with and without aura. One VBM study in particular showed a GM volume decrease in V5 in migraineurs with respect to controls, which correlated with disease activity; another found decreased GM volume in the left V1/V2 area and cerebellum. These findings, together with the sub-analyses we conducted in which migraine presence was included as a covariate, seem to suggest that our opposite results of increased GM volume in VSS patients are due to the visual snow condition alone.

Limitations

The absence of a correlation between morphological changes and clinical features of VSS is an issue. This may be due to the absence of an objective and reliable instrument to measure the severity of the condition. However, as visual snow syndrome is a relatively homogenous condition, and having selected a patient population with similar clinical features, we suggest that the
morphological changes that emerged from this study can be generalized to a larger number of patients. Given that eye dominance was not routinely tested as part of the study, it is not possible to exclude its effect on the laterality of the morphological changes found within the visual cortex. However, given that GM increases appeared bilaterally when the significance threshold was lowered, it is more likely that this finding was due to low statistical power.

Conclusions

Our study confirms that the neurological syndrome of visual snow is characterized by subtle anatomical brain changes in affected patients. These morphological grey matter alterations involve relevant neocortical visual areas pertaining to motion pathways, as well as important cognitive and attentional cerebellar areas, and seem to represent an inherent trait of the condition. These abnormalities could partially explain the functional changes found through other neuroimaging techniques in visual snow syndrome, and potentially some of its clinical elements as well. Our results provide further insight into a relatively unknown condition, creating the basis for future investigations in the disorder. This is a necessary step in order to provide optimal treatment strategies for patients, either pharmacological or neuromodulatory, which are currently lacking.
## Appendix 1: Authors

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<tr>
<td>Francesca Puledda, MD</td>
<td>King’s College</td>
<td>Designed and conceptualized the study; acquired, analysed and interpreted the data; drafted the manuscript for intellectual content</td>
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<td>Muriel Bruchage, PhD</td>
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<td>King’s College</td>
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<td>Dominic Ffytche, MD, PhD</td>
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<td>Steve CR Williams PhD</td>
<td>King’s College</td>
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<td>Peter J. Goadsby, MD, PhD</td>
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The authors would like to thank all the patients who took part in the study. This research would not have been possible without their participation and support.
References


Figure legends

Figure 1. *Grey matter volume increase in the left visual cortex in visual snow syndrome.*

Left primary visual cortex increases in grey matter (GM) volume in VSS patients respect to controls (x = -2, y = -98, z = 3; k = 594; p = 0.007 uncorrected, *p* = 0.06 FWE). Results are from whole-brain analysis; GM volume differences between groups are outlined over T1 images. Bar represents *T*-values.
Figure 2. *Changes in cerebellar grey matter volume in visual snow syndrome.*

a) Area of cerebellar grey matter volume increase in VSS patients (x = -12, y = -62, z = -23; k = 25; \( p = 0.02 \) FWE). GM volume differences between groups are outlined over parcellated cerebellar T1 images. Bar represents \( T \)-values.

b) Cerebellar flatmap of plotted \( T \)-values from VSS patients respect to controls (obtained from SUIT within SPM12), with labels for anatomical regions. Bar represents \( T \)-values.
Figure 3. *Summary of cortical volumetric changes in patients with visual snow syndrome, as shown by voxel-based morphometry.*

Render illustration of the three brain regions of increased grey matter volume in patients with visual snow syndrome, respect to healthy controls. Left V1 cluster is illustrated in green; left V5 cluster in blue; left cerebellum cluster in red. For statistical values of each area, see full text. Image was created in MRICroGL and superimposed on standard brain template.
Table 1. Demographic and clinical characteristics of patients with visual snow syndrome.

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<td>BW,C,F,T</td>
<td>+ + + + + + + + + + + +</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>22</td>
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<td>BW</td>
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<tr>
<td>21</td>
<td>M</td>
<td>35</td>
<td>33</td>
<td>BW</td>
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<td>19</td>
<td>#</td>
<td>BW</td>
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<td>M</td>
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<tr>
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<td>M</td>
<td>30</td>
<td>#</td>
<td>BW,F</td>
<td>+ + + + + + + + + + +</td>
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Salbutamol inhaler, multivitamins, Paracetamol PRN, Magnesium Paracetamol PRN, Levothyroxine, CQ10, Fluticasone nasal spray

# = Symptoms present for as long as patient could recall; + = present;
BW = black and white static; C = coloured static; F = flashing static; T = transparent static;
A = Afterimages; T = Trailing; B = blue-field entoptic phenomena; FL = floaters; SL = self-light of the eye; FLA = flashes; NY = nyctalopia; PH = Photophobia; MIG = migraine; TIN = tinnitus;
OCP = oral contraceptive pill; PRN = pro re nata (i.e. when necessary)
Table 2. Areas of grey matter volume increase in patients with visual snow syndrome \((n = 24)\) compared to healthy volunteers \((n = 24)\). FWE = family wise error correction. \(k\) = voxel size.

<table>
<thead>
<tr>
<th>Region</th>
<th>(p) (FWE)</th>
<th>(T)-value</th>
<th>(k)</th>
<th>MNI coordinates</th>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>(x) (y) (z)</td>
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<tr>
<td>Left V1</td>
<td>0.04</td>
<td>4.06</td>
<td>22</td>
<td>-3 -94 0</td>
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<tr>
<td></td>
<td>0.03</td>
<td>3.95</td>
<td>33</td>
<td>-6 -90 4</td>
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<td></td>
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<td>12</td>
<td>-9 -87 0</td>
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<td></td>
<td>0.04</td>
<td>3.56</td>
<td>16</td>
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<tr>
<td>Left V5</td>
<td>0.04</td>
<td>3.52</td>
<td>32</td>
<td>-38 -75 4</td>
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<tr>
<td>Cerebellum Crus I/lobule VI</td>
<td>0.02</td>
<td>4.86</td>
<td>25</td>
<td>-12 -62 -23</td>
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Occipital cortex and cerebellum grey matter changes in visual snow syndrome
Francesca Puledda, Muriel Bruchhage, Owen O'Daly, et al.
Neurology published online August 5, 2020
DOI 10.1212/WNL.0000000000010530

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