Severe, persistent visual impairment associated with occipital calcification and coeliac disease

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Keywords: Coeliac disease, occipital calcification, visual acuity, colour vision, motion perception, magnetic resonance imaging

Word count

Abstract: 181 words
Main text: 3150 words
Number of Figures: 3

ABSTRACT

While coeliac disease is primarily a disease of the digestive system, there have been several reports of neurological effects, both motor and cognitive. Here, we present the case of a woman with coeliac disease, under dietary control, in whom there is profound long-standing visual disturbance including reduction of visual fields, loss of rapid flicker and colour sensitivity and severe deficits in acuity. Structural magnetic resonance imaging (MRI) indicates large regions of calcification and abnormal tissue that is restricted to the occipital cortex, particularly the posterior region. Functional MRI indicates an absence of normal visual activation in the primary visual cortex, but at least in one hemisphere, there is neural activity to moving stimuli in visual motion area hMT+. White matter microstructure in the pathway between the lateral geniculate nucleus and hMT+ is normal compared to healthy control subjects, but is severely abnormal between the lateral geniculate nucleus and primary visual cortex. This case study illustrates the very specific nature of cortical deficit that can arise in association with coeliac disease, and highlights the importance of early dietary control for the disease.

1. INTRODUCTION

Coeliac disease (CD) is an autoimmune disease affecting the duodenum and jejunum, manifesting as intolerance to wheat products in the diet. Diagnoses of CD have become more common as awareness of the disease has increased. Recently, there has been greater recognition of the neurological implications of the disease, particularly those affecting the motor system [7] In a group of patients with biopsy confirmed coeliac disease, there was significantly lower cerebellar volume in addition to a decrease in grey matter volume within the cortex [4]. This reduction in cerebellar volume may explain the prevalence of ataxia in such neurological reports, reviewed by Hadjivassiliou and colleagues [8].

In contrast to the growing numbers of reports of motor impairment in coeliac disease, there are relatively few reports of specific sensory disturbance. An early report investigating the presence of bilateral occipital calcifications and epilepsy found a high prevalence of coeliac disease within this population [10]. Additionally, a series of three patients was described by Pfaender et al. [13], in which all patients had visual disturbance due to the epilepsy, but no chronic visual deficits. The link between coeliac disease, occipital calcification and occipital epilepsy is also considered by Taylor et al. in a review of occipital epilepsy [14]. While each of these studies has considered the occipital calcification, imaging has relied on low resolution computed tomography (CT) images and there has been little consideration of any long term visual impairment unrelated to the occipital epilepsy.

Here we present the case of a patient with severe, chronic visual disturbance associated with coeliac disease. Using detailed magnetic resonance imaging (MRI) of the occipital cortex we demonstrate the specific involvement of grey and white matter tissue of the early visual areas compared to healthy control subjects. Furthermore, these areas showing structural damage do not appear to respond to visual stimuli as measured using functional fMRI.

2. METHODS

2.1 Patient case history and control subjects

The patient (CD1) is a 54 year old woman, diagnosed with CD at the age of 19 following a history of weight loss, fatigue, and migraines. CD1 gave written informed consent prior to participation, and the study was granted ethical approval from *Oxfordshire REC (08/H0605/156)*. Neurological history: CD1 experienced migrainous visual aura and some absence attacks without aura from the age of 6. Although she was treated with epanutin and phenobarbitone she experienced very few seizures and none at all from the age of 8. We have not been able to review electroencephalograms from this period but have noted comments in clinic letters. At age 7 a Paediatrician commented that "The EEG showed clinical evidence of epilepsy of Petit Mal type" without describing the findings in detail. At age 13 another Paediatrician noted "She is still having fairly frequent migraine headaches but no signs of her epileptic equivalents. Her latest electroencephalogram however does show the record still to be unstable.". Anticonvulsants were discontinued at age 15 without recurrence of attacks. From the age of 6 she experienced episodes of classical migraine with visual aura but not since age 19. Aged 15, she noticed problems with her vision; she was unable to identify or to distinguish male and female faces and her reading performance deteriorated. She was observed to hold text very close when reading. Subjectively, visual function had remained static since she commenced a gluten free diet at age 19. Ophthalmological history: On ophthalmological examination CD1 has never worn glasses and is emmetropic on retinoscopy. She uses magnification for reading. Fundus examination, optical coherence tomography and autofluorescence examination of the retina revealed no abnormality. Electroretinogram (ERG) including pattern ERG (International Society for Clinicale retinarescence examination standard) was also normal. CD1 developed with normal vision into her teens and does not show any evidence of nystagmus. She demonstrates accurate fixation on targets. CD1 also has rheumatoid arthritis. Neuropsychological evaluation, unchanged between age 25 and 54, revealed that Verbal IQ was high average and Performance IQ was low average, likely due to the visual impairment.

Twelve control subjects (6 females, age range 21-74, mean 46 yrs) were recruited as part of a related study investigating the visual function in hemianopia due to stroke. The control subjects did not perform any of the behavioural tests, but participated in a single MRI session.

2.2 Behavioural testing

Basic clinical tests of visual function included Goldmann perimetry, Snellen acuity and Ishihara plates. In addition, a range of detailed visual tests were performed with CD1 in the Applied Vision Research Centre, City University London. These included Landolt ring stimuli for accurate assessment of visual acuity and binocular examination of the visual field loss using laser generated spots on a uniform screen. Sensitivity for motion was investigated binocularly using moving stimuli of varying luminance contrast and speed. The movement was diagonally across a square region defined by either static or dynamic luminance contrast noise. The subject's task was to report the end point of target movement as top right, top left, bottom right or bottom left. This was achieved by pressing one of four response buttons arranged to correspond to the corners of a square.

Rapid flicker sensitivity was measured with binocular disc stimuli of 30' arc diameter at the fovea and diagonally in each of the four quadrants, some 6^{o} in the periphery. A five-alternative, forced–choice procedure was employed and each stimulus was modulated sinusoidally at either 10 or 15 Hz. The patient's task was to press one of five buttons to indicate the location of the stimulus.

Higher visual function was tested using fragmented letters and visuospatial tasks such as dot counting and reaching for targets across the visual field [9, 16]. Object identification based on typical and atypical views was also performed [17]

2.3 Magnetic resonance imaging

2.3.1 Data acquisition

MRI data were acquired using a 3T Siemens Trio scanner at the Oxford Centre for Clinical Magnetic Resonance Research (OCMR). CD1 and control subjects participated in a single scan session that included structural, diffusion-weighted and functional MRI scans. T1- and T2-weighted structural images were acquired at a resolution of 1 x 1 x 1x mm^3 and 0.34 x 0.34 x 5.2 mm^3 respectively. Whole head diffusion imaging was acquired at 2 x 2 x 2mm^3 (60 directions, b-value 1000 s/mm^2, 65 slices, TR=9.3 s, TE = 94 ms) [15]. Echo planar imaging (EPI) was performed during presentation of two different experiments using moving dots. In experiment 1, moving dots (30°/sec; white, 57.5 cd/m^2 on black background, 1.9 cd/m^2), subtending 8°, were presented centrally in a block design (16 s moving; 16 s stationary) for 8 repeats. Subjects were instructed to fixate a central white cross extending 0.5° x 0.5°. In experiment 2, an 8° patch of moving

dots (30°/sec; white, 57.5 cd/m^2 on mid-grey background, 17.8 cd/m^2), was presented either in the left or right hemifield, centered 7.5° from fixation. A fixation condition with neither stimulus present was used as baseline. In all conditions, a red fixation cross 0.5° x 0.5° was present. The three conditions were presented pseudo-randomly in a block design (16 s blocks; 6 repeats of each block). Although it was not possible to measure fixation objectively, CD1 has good fixation in behavioural tasks and reported being able to use a combination of the fixation markers and the centre of the screen to maintain correct fixation. For both EPI experiments data were acquired at 3 x 3 x 3mm^3 (48 axial slices, TR = 2; TE = 49 ms) from CD1 and a control group of 12 age-matched participants.

2.3.1 Data analysis

Measures of fractional anisotropy (FA) and mean diffusivity (MD) were extracted from the diffusion-weighted data using tools from FMRIB's software library (www.fmrib.ox.ac.uk/fsl). Deterministic fiber-tracking was performed using the MRtrix package (J-D Tournier, Brain Research Institute, Melbourne, Australia, http://www.brain.org.au/software [15]. Data were acquired from CD1 and 5 of the age-matched control subjects for comparison (4 F; age range = 45-60, mean 52.4 yrs).

Masks for the lateral geniculate nucleus (LGN), V1 and motion area hMT+ were derived from the Juelich histological atlas [11], and used as seeds for the fiber tracking. To quantify values for FA and MD, the mean value was extracted from tracts between LGN and V1 and LGN and hMT+ for each individual participant. The value for each voxel was weighted by the number of tracts passing it, so that voxels at the centre of the tract had a greater influence on the mean value. Statistics for determining whether CD1 differed from the control group used the method of Crawford et al. [3].

EPI data were analyzed using FMRIB's easy analysis tool (FEAT), another tool from FMRIB's software library. Images were pre-processed using a number of steps: head movement correction using MCFLIRT, spatial smoothing with a Gaussian kernel full-width, half-height (FWHM) – 5mm, mean-based intensity normalisation and non-linear high-pass temporal frequency filtering (Gaussian-weighted straight line fitting with sigma = 30s). EPI images were registered to the subject's own T1-weighted structural imaging using FLIRT.

Data from control subjects were combined using mixed-effects analysis in MNI space.

3. RESULTS

3.1 Behavioural results

CD1 has significantly decreased visual fields determined with Goldmann perimetry, which revealed inferior homonymous quadrantanopic scotomas to both static and kinetic targets (Figure 1A). Consistent with this, binocular examination of the visual field, using laser targets on a uniform screen revealed a complete loss of visual function below the horizontal meridian, extending down approximately 25° and ±28° horizontally. Beyond these limits, in the periphery, detection of this stimulus was normal although the isopters for the I4e and III4e targets on kinetic Goldmann testing were slightly reduced (Fig 1). Mean values for normal isopter position are shown in blue and red respectively, based on the work of Niederhauser & Mojon [12]. Indeed, also consistent with the perimetry, CD1 was able to see moving, luminance contrast stimuli with almost normal motion thresholds, outside of the lower visual field. Luminance contrast thresholds for detection of first order coherent motion vary with stimulus size and eccentricity, but are not affected by the presence of static background. In contrast, they are strongly affected by random dynamic noise in healthy subjects [1]. Consistent with previous findings in healthy subjects, static noise did not affect the patient's thresholds for motion detection, but dynamic noise caused these thresholds to increase monotonically with noise amplitude from 5% in the absence of spatial noise to 9 and 15% luminance contrast for dynamic noise of 12% and 24%, respectively. The similarity of these findings to healthy subjects suggests the involvement of a bandpass temporal mechanism that responds to first order motion, but remains unaffected by static noise [1].

CD1 was unable to detect any rapid flicker in the lower quadrants, even with 100% luminance contrast. At the fovea, 60% contrast was required for detection, while the respective figures for left and right upper quadrants were 19.9% and 16.7%. Normal thresholds are around 4%.

Acuity measured with Snellen charts was 6/60 in both eyes. Her binocular visual acuity, using Landolt ring stimuli, corresponded to a decimal visual acuity of 0.06. Reading ability was poor, with large letters and a magnifying glass required to manage very slow reading. She made no errors, however, on the Ishihara plates.

Tests of higher visual function revealed normal performance on fragmented letters and visuospatial tasks such as dot counting and reaching for targets across the visual field. She was impaired on face recognition but it is difficult to exclude impaired acuity as

being the cause of this. While she performed normally on identifying images of objects shown in typical views, she was impaired on identifying the same objects shown in atypical views. This indicates a higher-level object processing deficit that cannot be accounted for by reduced visual acuity.

3.2. Structural MRI

T1-weighted and T2-weighted images are shown in Figure 1B. The extensive damage to the occipital lobe is evident at first glance. In the T2-weighted images there are extensive hyperintense regions, likely indicating gliosis and increased water content. Additionally, there are regions of very low signal, likely to reflect calcification. Both the grey, and the white matter are affected, with the arrow in the right column indicating severe disruption of the optic radiation bilaterally. The combination of hyperintensity on T2- and hypointensity on T1-weighted images indicates increased water content.

The specificity of the damage to the occipital lobe is evident in the sagittal view of the brain in the bottom row of the figure. The black arrow indicates the boundary between the affected and unaffected regions. Note that the most anterior portion of the Calcarine sulcus remains intact, explaining the maintained peripheral visual ability of CD1.

3.3 Diffusion MRI

Tracts in CD1 are shown in Figure 2A, left panel. Pathways were also generated in a group of 5 age-matched control subjects (mean 52.4 ± 6.6 yr; 4 female). Values for fractional anisotropy (FA) and mean diffusivity (MD) were generated for all tracts and compared between CD1 and the control group (Figure 2A). Values for FA and MD in CD1 were similar to the control group for LGN<->hMT+ pathways in both hemispheres. In contrast, the LGN <-> V1 pathways were considerably impaired, with significantly reduced FA (Right: $t = -7.3$; $p = 0.002$; Left: $t = -4.1$; $p = 0.015$) and increased MD (Right: $t = 13.3$; $p = 0.0002$; Left: $t = 4.8$; $p = 0.009$;) [3], both markers of decreased integrity. The differences were particularly marked in the right hemisphere.

3.4 Functional MRI

All fMRI data are shown in Figure 3, both as slices and projected onto the surface of an average brain. Presentation of centrally presented moving dots in experiment 1

('Central Motion') led to significant activation (shown in blue) in anterior, ventral V1 bilaterally and hMT+ in the left hemisphere (center of cluster: -46, -72, 2), and a much smaller cluster in hMT+ in the right hemisphere (center of cluster: 42, -64, 4). Additionally, a posterior region of the superior temporal sulcus was evident bilaterally, coordinates (left: -46, -52, 10; right: 62, -48, 10). In contrast, the activity from the control group is spread across the occipital cortex, including V1 and other early visual areas.

In experiment 2, when moving dots were presented to either the right or left visual field separately, there was no significant activation in CD1 when the stimulus was presented in the left visual field. The response of the left hemisphere to the moving stimulus in the right visual field is shown with the red-yellow colour scheme. Consistent with experiment 1, the greatest visual activity was located in anterior, ventral V1 and hMT+ in the left hemisphere. In control subjects, activity was present across the left occipital cortex, with some activity in hMT+ of the right hemisphere.

The percent BOLD signal change is shown at the right of the figure for both experiments, indicating the response levels within the masks defined by using the Juelich histological atlas. Relative to the very high signal levels in V1 of control subjects, there is very little, or no, activation in CD1's brain. In contrast, the signal level in hMT+ in the left hemisphere is equivalent to control subjects. The level of activity in right hMT+ is considerably lower, as would be predicted by the whole brain analyses shown in the rest of the figure.

4. DISCUSSION

Subject CD1 has long-standing, severe visual disruption, as measured by perimetry and visual acuity, in addition to higher-level visual function. Abnormalities in structural and functional MRI are consistent with the behavioural measurements and all approaches support the hypothesis that vision is worst in the central visual field below the horizontal meridian and best in the periphery.

The severity of the visual deficits is likely to be related to the considerable involvement of V1, particularly the region corresponding to foveal vision. Indeed, the considerable damage to the foveal regions of early visual cortex likely led to the considerably elevated thresholds for detecting high contrast flicker. There is no apparent activity in the dorsal part of V1 that would represent the lower visual field. The spared peripheral vision is likely to reflect the anterior portion of V1 that extends beyond the damage (Figure 1).

Furthermore, all the evidence suggests that motion area hMT+ is reasonably intact, at least in the left hemisphere. In left hMT+ there is a lack of obvious structural damage to grey or white matter, fMRI activation to moving dots is strong and white matter microstructure is comparable to control subjects. In the right hemisphere, however, there is little fMRI activation and the grey matter structure appears abnormal. One point of discrepancy between the diffusion data and the fMRI data in the right hemisphere is that, although the microstructure of the LGN<->V1 pathway is considerably impaired, this does not appear to be the case for the LGN<->hMT+ pathway. The surface rendering of the activation to moving dots indicates some activation in the region of hMT+, suggesting that this minimal activity might be sufficient to prevent degeneration of the white matter tracts.

Throughout this study, probabilistic maps for hMT+, V1 and LGN from the Juelich histological atlas implemented in FSL [11] have been used to define the relevant structures both in CD1 and in the control subjects. The coordinates for all structures correspond well to those in the literature (e.g. [6, 18]). The use of these maps, which are generated from healthy brains, could be questioned. However, because the damage to CD1's brain was restricted to the occipital lobe, there were no registration issues. Furthermore, since the damage is believed to date from adolescence, global brain structure does not appear to be compromised.

Another point of interest regarding the fMRI motion responses is the presence of prominent activation in the superior temporal sulcus. This is an area not as significantly activated in the group response of control participants. Interestingly though, this region was also present in response to moving dots in agnosic patient DF who also has some damage to hMT+ [2]. It is possible, therefore that this region becomes more active when hMT+ is no longer functioning normally.

There are caveats to the study as the effects of calcification on the imaging contrasts is not yet established. Since the BOLD signal used to measure the fMRI activation is a T2*-weighted measure, the calcification is likely to cause artefact in the signal. It is possible therefore that there is some functioning tissue in the posterior occipital cortex, but that it cannot be detected with the current approach. Electrical measures of cortical activity such as EEG or MEG may be more interpretable for this purpose, although the spatial resolution is considerably lower in both cases.

While there have been several examples of occipital calcification associated with coeliac disease measured with CT, this is the first study to provide detailed characterisation of the visual deficits and functional imaging that supports the visual loss. Furthermore, the treatment for the coeliac disease did not improve visual function, as has previously been reported [5] although it may have stabilized the condition. This type of severe cortical visual damage, albeit rare, indicates the importance of early, and accurate diagnosis of CD.

ACKNOWLEDGMENTS

This work was funding by the Royal Society through a University Research Fellowship to HB. RM held a Medical Research Council Studentship and a Foulkes Fellowship.

Conflict of Interest Statement

On behalf of all authors the corresponding author states that there is no conflict of interest.

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Figure Legends

Figure 1. A shows the Goldmann perimetry for the left and right eyes. CD1 was unable to detect any targets in a region in the lower visual field, indicated by the black region. The corresponds to bilateral inferior homonymous quadrantic scotomas. Visual performance was reduced in the remaining field, although sensitivity for motion perception was least affected. Standard isopters for the targets used are shown as a blue line (III4e target) and a red line (I4e target) based on the fields shown in [12]. Note that the central 1° cannot be tested on the Goldmann perimeter rather than indicating macular sparing. B shows the extent of the structural damage to the occipital cortex. Both T1- and T2-weighted images show considerable regions of abnormal signal within the occipital lobe (white arrows). The damage is restricted to the occipital lobe as shown in the sagittal view in the bottom row (black arrow).

Figure 2. Diffusion tractography between the lateral geniculate nucleus (LGN) and cortical regions. A shows examples of tracts between LGN and hMT+ (red) and between LGN and V1+ (blue) in a healthy control subject and in CD1. In CD1 (black squares), the LGN<->hMT+ pathway is considerably stronger than LGN <-> primary visual cortex, while the opposite is true for the control subjects. The considerable effect of the occipital damage is reflected in the reduced fractional anisotropy (B) and increased mean diffusivity (C) in CD1 compared to control subjects (n = 5; error bars show standard errors).

Figure 3. Functional MRI responses to moving dots in CD1 and control subjects. The upper panel shows the significant activation to a moving dot stimulus in the center of the visual field (blue colour scheme). While the control group (n = 5; error bars depict standard errors) shows extensive activity within the occipital cortex, CD1 only shows activity in anterior, ventral V1, left hMT+, a small region of right hMT+ and bilateral superior temporal sulcus (STS). The lower panel shows the pattern of activation (red-yellow colour scheme) when a moving dot stimulus is presented in the right side of the visual field. Similar regions of the occipital lobe are active in this experiment. There was no significant activation in CD1's brain when the stimulus was presented in the left side of the visual field.

The graphs on the right of the figure show the percent BOLD change in response to the moving stimuli. The response in left hMT+ to both stimulus types is comparable to the healthy control subjects, while V1 activation levels are significantly lower in both

hemispheres. The BOLD signals for experiment 2 are for the left hemisphere (right hemifield motion) in controls and ‘CD1 left’. The ‘CD1 Right’ values are for the Left hemisphere motion.

Figure 1

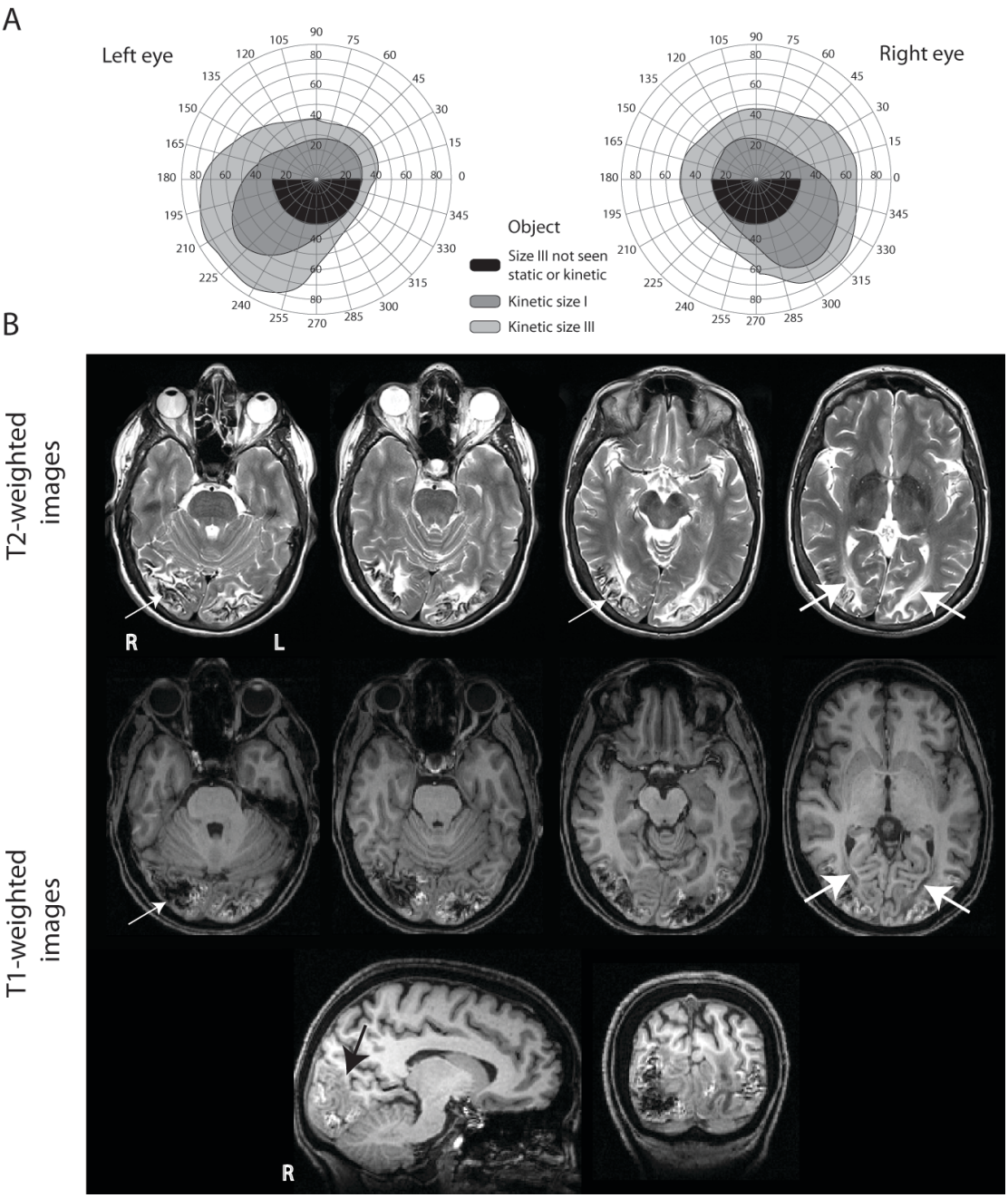

A
Left eye
Right eye
Object
Size III not seen static or kinetic
Kinetic size I
Kinetic size III
B
T2-weighted images
T1-weighted images
R
L
R

Figure 2

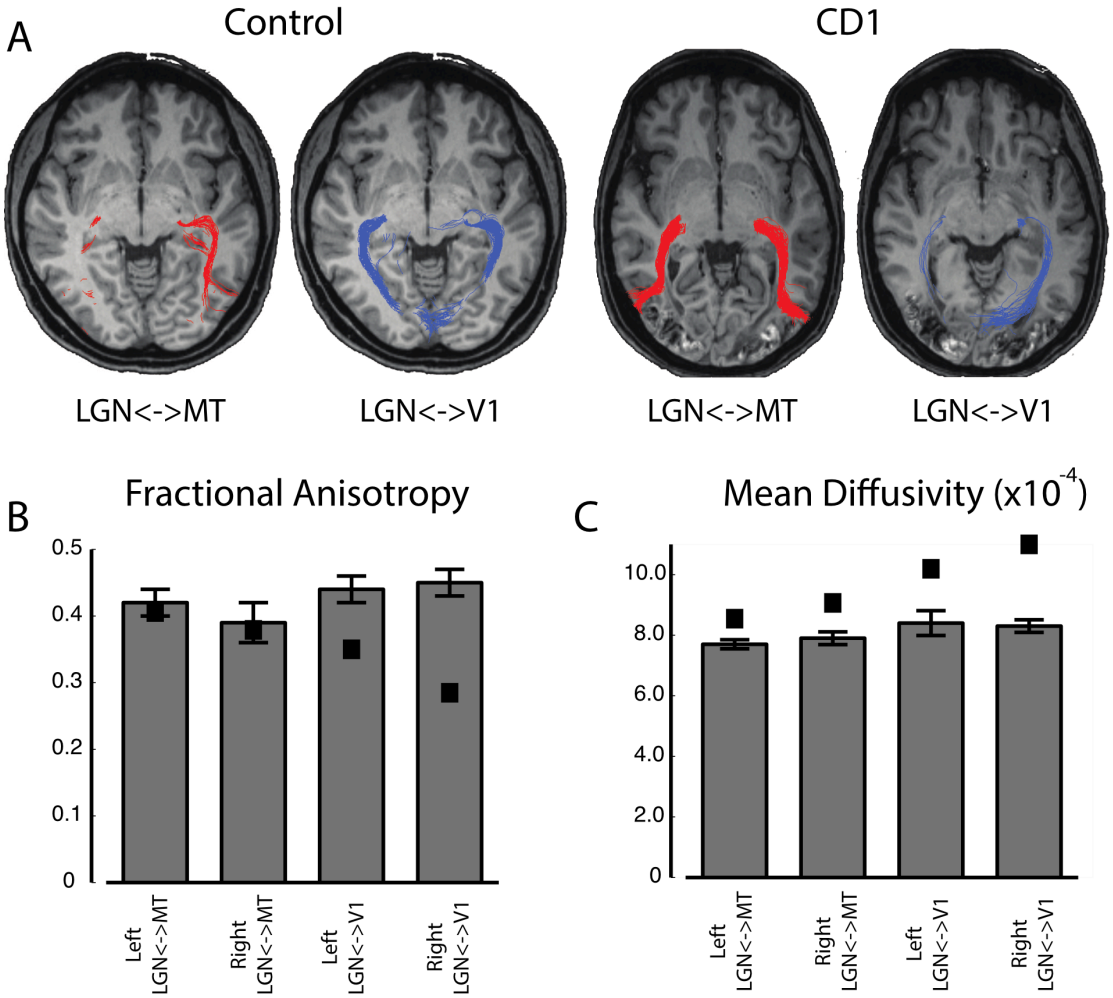
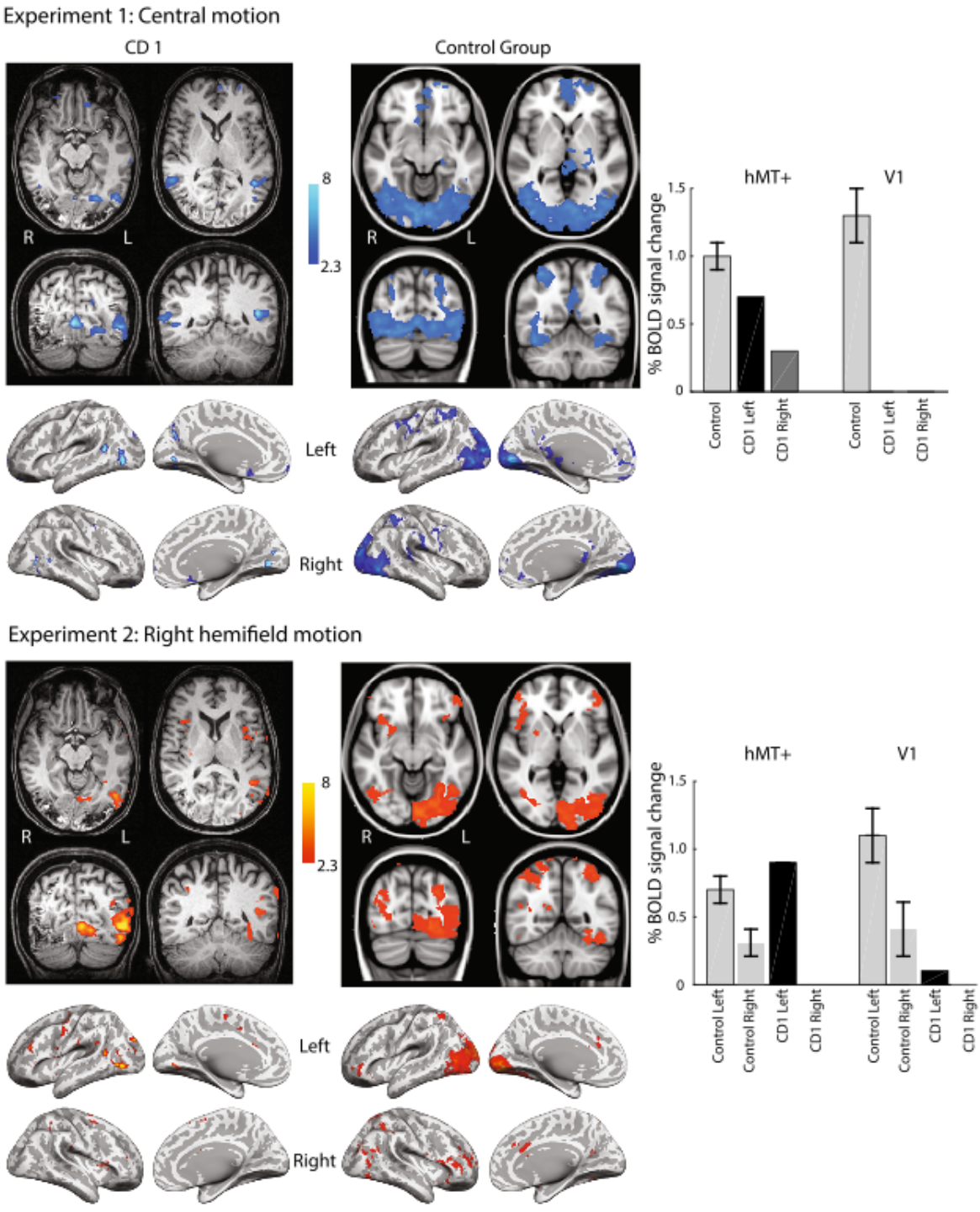

A
Control
CD1
LGN<->MT
LGN<->V1
LGN<->MT
LGN<->V1
B
Fractional Anisotropy
0.5
0.4
0.3
0.2
0.1
0
Left LGN<->MT
Right LGN<->MT
Left LGN<->V1
Right LGN<->V1
C
Mean Diffusivity (x10-4)
10.0
8.0
6.0
4.0
2.0
0
Left LGN<->MT
Right LGN<->MT
Left LGN<->V1
Right LGN<->V1

Figure 3


Experiment 1: Central motion
CD 1
Control Group
R
L
8
2.3
Left
Right
hMT+
V1
% BOLD signal change
1.5
1.0
0.5
0
Control
CD1 Left
CD1 Right
Experiment 2: Right hemifield motion
Control Left
Control Right