V1 Projection Zone Signals in Human Macular Degeneration Depend on Task Despite Absence of Visual Stimulus

Highlights

- V1 LPZ responses to visual stimuli were found only in the task condition.
- V1 LPZ also responds to tactile and auditory stimuli only in the task condition.
- The task-dependent V1 LPZ responses are modality independent.
- V1 LPZ responses can be evoked by task-related feedback signals.

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In Brief

Masuda et al. show that V1 lesion projection zone of JMD patients responds to tactile and auditory stimuli only in the one-back memory task, not in the passive condition. The modality-independent, task-dependent V1 LPZ responses suggest that V1 LPZ responses reflect task-related feedback signals rather than reorganized feedforward signals.
V1 Projection Zone Signals in Human MacularDegeneration Depend on TaskDespite Absence of Visual Stimulus

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SUMMARY

Identifying the plastic and stable components of the visual cortex after retinal loss is an important topic in visual neuroscience and neuro-ophthalmology.1–5 Humans with juvenile macular degeneration (JMD) show significant blood-oxygen-level-dependent (BOLD) responses in the primary visual area (V1) lesion projection zone (LPZ),6 despite the absence of the feedforward signals from the degenerated retina. Our previous study7 reported that V1 LPZ responds to full-field visual stimuli during the one-back task (OBT), not during passive viewing, suggesting the involvement of task-related feedback signals. Aiming to clarify whether visual inputs to the intact retina are necessary for the LPZ responses, here, we measured BOLD responses to tactile and auditory stimuli for both JMD patients and control participants with and without OBT. Participants were instructed to close their eyes during the experiment for the purpose of eliminating retinal inputs. Without OBT, no V1 responses were detected in both groups of participants. With OBT, to the contrary, both stimuli caused substantial V1 responses in JMD patients, but not controls. Furthermore, we also found that the task-dependent activity in V1 LPZ became less pronounced when JMD patients opened their eyes, suggesting that task-related feedback signals can be partially suppressed by residual feedforward signals. Modality-independent V1 LPZ responses only in the task condition suggest that V1 LPZ responses reflect task-related feedback signals rather than reorganized feedforward visual inputs.

RESULTS

We first confirmed a large bilateral absolute central scotoma in both eyes of juvenile macular degeneration (JMD) patients by Goldmann perimetry (Figure 1; Table S1). We then measured fMRI responses using tactile and auditory stimuli for these patients (see STAR Methods for details). To assess the task dependence of the blood-oxygen-level-dependent (BOLD) responses, we employed two conditions: passive and one-back task (OBT) conditions. To eliminate any retinal inputs, participants were instructed to close their eyes during the experiment.

Figure 2 shows the responses to the tactile stimuli for a representative JMD patient and control participant (JMD1 and C1), and Figure S1A describes results in other JMD patients. In the passive condition, the tactile response for both JMD1 and C1 was found in the postcentral gyrus, which corresponds to the primary somatosensory cortex (S1).8–11 The occipital areas did not respond to tactile stimuli for both JMD1 and C1. In contrast, the responses in the OBT condition for JMD1 and C1 differed from those in the passive condition. The S1 responses were stronger and the above-threshold region covered a larger area than in the passive condition.12 Occipital areas of C1 responded negatively,13,14 though they were not consistent across controls. On the contrary, occipital areas of JMD1 exhibited large activation in the OBT condition. Other JMD patients showed a similar pattern of results (Figure S1A), except for JMD5, who had no primary visual area (V1) responses in either condition.

Figure 4A shows the amplitude of response quantified by phase-specified coherence7,15–17 averaged across JMD patients or normal controls. Two-way repeated-measures ANOVA on the V1 response amplitude indicated a significant main effect of the task (F (1,10) = 6.24; p = 0.032), although the main effect of the participant group was insignificant (F(1,10) = 3.48; p = 0.092). The interaction between task condition (control versus OBT) and participants’ group (JMD versus control) was marginally significant (F(1,10) = 4.61; p = 0.058). Tests of simple main effects indicated that the effect of task on V1 responses was significant for...
the JMDs (F(1, 10) = 10.78; p = 0.008), but not for the controls (F(1, 10) = 0.06; p = 0.809).

We then calculated the activation in visual areas, including V2, V3, hV4, TO1,19 and frontal eye field (FEF) (Figures 2, bottom panels, and 4A). The activation during the tactile OBT was modest in V2 and could not be detected in other visual areas, including V3, hV4, and TO1. Weak responses in FEF were observed during the OBT. Two-way repeated-measures ANOVA showed that the main effect of the task was marginally significant in FEF (F(1, 10) = 4.63; p = 0.057). Other details of the ANOVA are shown in Table S3.

Figure 3 shows the responses to the auditory stimuli for JMD1 and C1 (see Figure S1B for the results of other patients). In the passive condition, the auditory responses for both JMD1 and C1 were found in the transverse temporal gyrus and superior temporal gyrus, which correspond to the primary/secondary auditory cortex (A1/A2).19,20 Contrary to the stimulus-evoked responses in the A1/A2, no (JMD1) or weak negative (C1) responses11,22 were observed in V1. In the OBT condition, the strongest activation was again found in the A1/A2, which was larger than in the passive condition. Activations in the occipital areas were very different from those in the passive condition. Although no activation was observed in V1 for C1, positive V1 activation was found for JMD1. The response time course clearly indicates that auditory-evoked responses in V1 were observed only in the OBT condition, not in the passive condition for JMD1.

Figure 4B shows the phase-specified coherence averaged across JMD patients and normal controls. Two-way repeated-measures ANOVA on V1 responses indicated significant main effects of both participant groups (F(1, 10) = 25.88; p < 0.001) and task (F(1, 10) = 32.26; p < 0.001). Although the interaction between task (control versus OBT) and participants group (JMD versus control) was insignificant (F(1, 10) = 0.05; p = 0.826), the effect of the task on V1 responses was qualitatively different between patients and controls. Specifically, the task changed V1 responses from negative to zero for the controls; the task changed V1 responses from zero to positive for the patients (significant interaction for the ANOVA on the absolute value of V1 responses supports this qualitative difference; F(1, 10) = 22.59; p < 0.001). Although the functional roles of the negative V1 responses in the passive condition for control participants remain to be seen,11,23–26 the positive V1 responses of JMD patients in the OBT condition for auditory stimuli are fully consistent with those for visual or tactile stimuli. ANOVA for other visual areas suggested that the auditory-evoked responses in the OBT condition for JMD patients were rather common across visual areas (Table S3).

To test whether the complete absence of visual inputs is critical for the tactile/auditory-task-related responses in V1, we measured the responses to the tactile/auditory stimuli with eyes open (Figure S2). Although the results are overall similar to those in the eyes-closed condition (Figure 4), the task-dependent activity in V1 of JMD patients was weaker or nearly absent for auditory stimuli (see Table S4 for details). We then statistically assessed the differences in task-dependent activations of V1 in JMD patients between eyes-closed and eyes-open conditions. There was no significant difference in tactile-evoked V1 responses of JMD patients in OBT condition between eyes-open and eyes-closed conditions (two-tailed paired t test; t(5) = 1.12; p = 0.312). Auditory-evoked V1 responses of JMD patients in OBT condition were greater in eyes-closed condition as compared with eyes-open condition (two-tailed paired t test; t(5) = 3.01; p = 0.030). Given the similar OBT performance between eyes-open and eyes-closed conditions (Table S2; 95.1% ± 5.0% and 94.7% ± 5.0% [mean ± SEM], respectively), these results indicate that task-dependent V1 responses to auditory stimuli were suppressed by the presence of the visual input and may not be explained by differences in attentional demands or arousal. These results suggest that the complete absence of visual inputs is not necessary but enhances the task-dependent V1 responses in JMD patients, particularly for auditory stimuli.

The aforementioned analyses (Figures 2, 3, and 4) showed task-dependent V1 responses averaged across 30 deg of the visual field, which roughly correspond to the lesion projection zone (LPZ) (Figure 1). To further clarify the relationship between V1 responses and the LPZ,27 we finally assessed V1 responses and the percentage of intact visual fields as a function of eccentricity (Figures S3 and S4 for eyes-closed and eyes-open conditions, respectively). The tactile/auditory-task-dependent BOLD responses tend to be the most prominent in the foveal V1 corresponding to the LPZ (especially for JMD1), although they extend into the intact visual fields for some patients (e.g., JMD2 and 3 in the eyes-closed condition of the tactile stimuli).
DISCUSSION

Over the last several decades, the interpretation of neural responses in V1 LPZ after the retinal lesion has been actively debated. Some investigators proposed that responses in V1 LPZ are explained by cortical remapping mediated by axonal sprouting. According to this hypothesis, the cortical response in LPZ should depend on properties of feedforward connections. However, experiments and simulations have shown that the cortical response in LPZ is a result of synaptic plasticity, and not due to the remapping of the visual cortex. Therefore, it is important to consider other factors that may contribute to the response in LPZ, such as the activation of the nervous system in response to the visual stimulus. Overall, the interpretation of neural responses in V1 LPZ after the retinal lesion has been actively debated, but further research is needed to understand the underlying mechanisms.
sensory inputs rather than task demands. In the human fMRI literature, although no significant responses in LPZ were initially reported,6,16,40 other studies reported large BOLD responses in V1 LPZ of JMD patients.6,41,42 Interpretation of these responses has been debated because the responses can be explained by remapping driven by axonal sprouting or plastic change in the visual system earlier than V1,6 a subset of neuronal populations with a large receptive field covering intact visual field5,16 or top-down feedback signals.6,43 Later, Masuda et al.7 found that JMD patients showed significant BOLD responses in LPZ only when they were performing a stimulus-related task, leading to the hypothesis that V1 LPZ responses could be explained by task-dependent feedback signals, which are ordinarily suppressed by feedforward signals in control participants. If feedback signals mediate task-dependent response in V1 LPZ, such feedback signals should (1) be independent of stimulus modality, (2) become profound after experiencing the lack of feedforward sensory inputs, and (3) be ordinarily suppressed in control participants with feedforward signals to V1.

In fact, here, we found that task-dependent V1 LPZ responses were observed not only for visual stimuli but also for tactile and auditory stimuli. Furthermore, Merabet et al.44 demonstrated an increase in BOLD responses within the occipital cortex of normally sighted participants during a tactile discrimination task after 5 days of complete visual deprivation. In contrast, Baker et al.41 reported that two macular degeneration patients with foveal sparing did not show task-dependent responses in the occipital pole, suggesting that complete absence of functional foveal vision is necessary for LPZ responses. These results suggest that task-dependent feedback signals can activate the occipital cortex without corresponding afferent inputs, not only in macular degeneration patients but also in normally sighted participants; the activation becomes prominent only after a complete loss of foveal input by disease or artificial visual deprivation.

Our previous work using visual stimuli ascribed the absence of V1 responses in controls to the zero-contrast feedforward signals balanced with task-related feedback signals with OBT.7 A lack of V1 responses in controls, together with substantial responses in JMDs, to tactile/auditory stimuli when they closed eyes may be explained by the original hypothesis. The zero-contrast feedforward signals should remain in control participants when they closed their eyes, although these signals are absent in the JMD patients with retinal damage. For this reason, the LPZ of JMDs is missing the zero-contrast feedforward signals, and this may permit V1 LPZ responses from other modalities and during the OBT. There are other possible mechanisms, of course. For example, feedback signals and non-visual signals to the LPZ may become more prominent in JMD patients as compared with controls. Distinguishing these possibilities requires further understanding of the cortical origin of the feedback and non-visual signals, as we discuss below.

Although speculative, the FEF is one candidate area that generates task-related, modality-independent feedback signals to V1, given converging evidence for the role of FEF on generating top-down signals to the visual cortex15–50 including an fMRI study on blind participants.51 Our data also demonstrate that FEF showed modest activity during OBT for tactile and auditory stimuli (Figure 4). Given that the task-dependent responses were less pronounced in extrastriate visual areas, especially for tactile stimuli, the feedback signals might project directly toward V1, not the other visual areas. Still, this hypothesis is speculative because we have not proven the signal flow between FEF and V1. It is also not yet clear whether feedback signals observed in this study are common with those reported in visual attention studies because the task is different and the effect of attention on visual areas along the hierarchy was variable across studies.53–57

Previous studies suggested preserved retinotopic organization in V1 of JMD patients58 and congenital bilateral anophthalmia.59 Consistent with this idea, the task-dependent V1 LPZ
responses of JMD patients observed in this study suggest preservation rather than remapping of retinotopy. The present results also suggest the preservation of overall responsiveness and feedback signals in V1 of JMD patients. These results provide promising implications on the cortical prosthesis, which enables the reconstruction of visual experience, making use of intact neural tissue and preserved retinotopic organization.\(^{10}-^{42}\)

Although many previous studies reported tactile- or auditory-evoked V1 responses in blind patients,\(^{43}-^{46}\) they did not assess the task dependency of responses. JMD patients have preserved visual fields, enabling us to assess the impact on intact feedforward signals. In fact, V1 responses of JMD patients evoked by auditory OBT were greater in eyes-closed than in eyes-open condition, suggesting suppression of task-dependent auditory responses by visual inputs. Therefore, we revealed novel observations supporting the hypothesis that top-down, modality-independent signals are ordinarily suppressed by feedforward signals and become profound in the absence of retinal inputs.

To summarize, we studied how OBT affects BOLD responses to tactile and auditory stimuli for both JMD patients and control participants. V1 did not respond in the passive condition for both groups of participants. Substantial V1 responses were observed in several JMD patients during the task condition. Our results indicate that task-related feedback signals, not visual input itself, are crucial for V1 LPZ response. The deletion of feedforward input from the retina may unmask pre-existing task-dependent cortical signals that are ordinarily suppressed by the deleted signals.

**STAR METHODS**

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**SUPPLEMENTAL INFORMATION**

Supplemental Information can be found online at https://doi.org/10.1016/j.cub.2020.10.034.

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**AUTHOR CONTRIBUTIONS**


**DECLARATION OF INTERESTS**

The authors declare no competing interests.

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**REFERENCES**


**STAR METHODS**

**KEY RESOURCES TABLE**

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| Deposited Data | Original/source data for figures | This paper [https://osf.io/rde2g/] |

**RESOURCE AVAILABILITY**

**Lead Contact**
Further information and requests for resources and reagents should be directed to and will be fulfilled by the Lead Contact, Yoichiro Masuda (ymasuda@jikei.ac.jp).

**Data and Code Availability**
Original/source data for figures in the paper is available at a public repository [https://osf.io/rde2g/].

**Materials Availability**
This study did not generate new unique reagents.

**EXPERIMENTAL MODEL AND SUBJECT DETAILS**

We report measurements from 12 participants; 6 participants with JMD (JMD1–6; see Table S1) and 6 control participants with normal vision (C1–6; 5 males and 1 female; ages 34–45). Recruitment of low-vision patients for basic research is difficult. Therefore, we have adopted methods that enable us to perform measurements of single-participants. This approach is also valuable for clinical applications in which decisions must be made about the status of individual JMD patients. Even though the number of participants is small for a group comparison approach, an N = 6 is comparable or larger than the N in previous fMRI studies on JMD patients. The limited statistical power on group comparison may not be a major concern in this work, since task-dependent V1 responses were visible in individual JMD patient level and the overall pattern in the single-participant analysis was well replicated in two different sensory modalities (tactile and auditory).

All JMD patients had a central scotoma originating from the damage of the bilateral foveal retina or macular retina. The JMD patients were diagnosed with one of two types of JMD: cone-rod dystrophy (CRD), or Leber Congenital amaurosis (LCA). The JMD patients had neither additional eye-related diseases nor any other neurological problems. JMD1, 4, 5, and 6 were diagnosed with CRD, an inherited progressive disease where cone photoreceptors deteriorate first, followed by deterioration of rod photoreceptors in which lipofuscins-like materials accumulate predominantly in the foveal retinal pigment epithelium. The symptoms include decreased visual acuity, decreased sensitivity in the central visual field, color vision defects, and photoaversion; these symptoms are followed by progressive loss in peripheral vision. The diagnosis of CRD is based on clinical history, fundus examination, and decline of full-field electroretinogram. JMD 2 and 3 were diagnosed with LCA, congenital onset disease but relatively stable after birth. The symptoms include decreased visual acuity and decreased sensitivity in the central visual field. The diagnosis of LCA is based on clinical history, fundus examination, and genetic examinations.

All procedures adhered to protocols based upon the world medical association declaration of Helsinki ethical principles for medical research involving human participants, approved by the ethical committees of Tamagawa University and Jikei University. All participants provided written informed consent to participate in the project.
METHOD DETAILS

Visual Field Perimetry
The visual fields of JMDs were measured by Goldmann perimetry (Figure 1). We used kinetic targets and defined the absolute visual field loss as the region in which they could not detect the highest contrast and largest size stimulus (1000 apostilb, size V, 1.72° diameter). The purpose of the perimetry measurements was to establish the region of the central visual field loss.

MR Stimuli
The tactile stimuli were piezo stimuli on the left index and middle fingers, while the auditory stimuli were tone bursts (261, 293, 329, 429, 392, 440, and 493 Hz). Stimuli were presented in a blocked design where blocks including the tactile or auditory stimulus and blank blocks were alternated. The duration of each block was 15 s. During the blocks with the tactile or auditory stimulus, piezo stimuli or tone bursts for 800 ms were repeatedly presented with an inter-stimulus-interval of 200 ms. The stimulation position of the piezo stimulus or pitch of the tone burst changed randomly across each presentation. Each run contained 10 stimulus blocks. The tactile and auditory stimuli were presented in separate runs.

To assess the effect of the task on the BOLD responses, we employed two conditions: passive and OBT conditions. In the passive condition, participants sensed stimuli passively without performing any tasks. In the OBT condition, participants responded when the same stimulus was repeated (a finger for the tactile stimuli or pitch for the auditory stimuli). The task performance of JMD patients was shown in Table S2.

For the purpose of assessing the effect of visual inputs, we employed eyes-closed and eyes-open conditions. In the eyes-closed condition, participants were instructed to close their eyes in the dark MRI scanner, which eliminates retinal inputs during the experiment. In the eyes-open condition, JMD patients and control participants maintained fixation using their preferred retinal locus or fovea, respectively, at a dot (2° diameter) placed at the center of the screen. In the eyes-open condition, the lights in the room were turned off.

The stimuli were generated in the MATLAB programming environment using the PsychToolbox70 running on a Windows XP computer. The tactile stimuli were presented using a piezoelectric tactile stimulus device (TI-1101, KGS Corporation, Japan). The auditory stimuli were presented using an MRI Audio system (Serena Sound, Resonance Technology Inc., USA). The visual stimulus (only fixation dot) was presented using an LCOS projector (WUX6000, Canon, Japan) in the eyes-open condition while the projector was turned off in the eyes-closed condition. Participants viewed the display through a mirror mounted above the head in the eyes-open condition.

Scanning Procedure
The MRI data were acquired on a 3-T Siemens Trio Tim scanner (Erlangen, Germany) at Tamagawa University Brain Science Institute, Machida, Japan. FMRI images were collected using a single-shot gradient echo-planar imaging sequence (37 planes; time repetition/time echo [TR/TE], 3000/36 ms; flip angle, 90°; voxel size, 2.0 × 2.0 × 2.0 mm; field of view [FOV], 192 mm). A structural T1-weighted MRI volume scan of the entire head was also obtained for each participant (voxel size, 1 mm isotropic).

Data Analysis and Visualization
Data were analyzed using the mrVista software (Stanford University, https://github.com/vistalab/vistasoft). The first 10 time frames in each functional run were discarded because of the start-up magnetization transients in the data. The remaining time frames were corrected for motion. No spatial smoothing was performed. The FMRI signals were converted to percentage signal change by dividing and subtracting each voxel’s time series by the time-series mean. Baseline drifts were removed from the time series by high-pass temporal filtering.

We measured the amplitude of the BOLD responses by calculating the phase-specified coherence of each fMRI time series. This quantity measures the BOLD response amplitude at the stimulus frequency and phase, adjusted for the hemodynamic delay. The precise formula for the phase-specified coherence is given in previous publications7.15–17. Briefly, we first estimate the stimulus-driven phase of the fMRI time course, which corresponds to hemodynamic delay, from the individual time course data with which the most reliable activations were found in sensory areas (S1 for tactile and A1/2 for auditory stimuli). We then calculated the phase-specified coherence in each ROI using the responses in this phase and at the stimulus alternation frequency. The values ranged between −1 and 1; positive values reflect stronger responses to the tactile/auditory stimuli, and negative values reflect stronger responses to the blank. We denote the in-phase and out-of-phase response as a positive or a negative BOLD response, respectively. The phase-specified coherence is advantageous as compared with the general linear model approach fitting canonical hemodynamic response function to BOLD time series because it can robustly estimate stimulus-locked positive and negative BOLD responses to the blank. We denote the in-phase and out-of-phase response as positive or negative BOLD responses, respectively.

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We performed segmentation between gray matter and white matter on structural T1-weighted images using an automated procedure in Freesurfer69. This segmentation was used to visualize cortical activations on the inflated representation of the white-gray matter boundary. We further identified the approximate position of visual areas using a surface-based probabilistic atlas72, which spans 30 deg of visual angle. We adapted visual areas defined in this atlas (V1, V2, V3, hV4, TO-1, and FEF) for the structural T1-weighted image in individual participants based on surface-based registration. We also used the retinotopy atlas proposed by Benson et al.71 to investigate the eccentricity dependency of V1 responses (from 0-10 deg to 70-80 deg in eccentricity).
QUANTIFICATION AND STATISTICAL ANALYSIS

Analyses of fMRI data were performed using mrVista [https://github.com/vistalab/vistasoft] running on MATLAB. ANOVA was performed using IBM SPSS. Data throughout the manuscript are presented by mean ± SEM. Details of n for each experiment is the number of participants. A p value of 0.05 was used to define significance.