Multisensory Cue Combination after Sensory Loss: Audio-Visual Localization in Patients with Progressive Retinal Disease

Sara E Garcia[1*], Pete R Jones[1], Eleanor I Reeve[1],

Michel Michaelides[1, 2], Gary S Rubin[1], Marko Nardini [3, 1*]

(1) University College London, UCL Institute of Ophthalmology, London, UK

(2) Moorfields Eye Hospital NHS Foundation Trust, London, UK

(3) Durham University, Department of Psychology, Durham, UK

* Corresponding authors

Email: sara.garcia.12@ucl.ac.uk, marko.nardini@durham.ac.uk

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Abstract

Human adults can combine perceptual estimates from different senses to minimize uncertainty, by taking a reliability-weighted average, (the maximum likelihood estimate, MLE). While research has shown that healthy human adults re-weight estimates as their reliability changes from one trial to the next, less is known about how humans adapt to gradual long-term changes in sensory reliability. This study assessed whether individuals diagnosed with progressive visual deterioration, due to retinal disease, combined auditory and visual cues to location according to optimal (MLE) predictions. Twelve patients with central visual loss, 10 patients with peripheral visual loss, and 12 normally sighted adults were asked to localize visual and/or auditory targets in central (1°-18°) and peripheral (36°-53°) locations. Normally sighted adults and patients with peripheral visual loss showed multisensory uncertainty reduction and cue weighting in line with MLE predictions. In contrast, patients with central visual loss did not weight estimates appropriately in either the center or the periphery, and failed to meet MLE predictions in the periphery. Our results show that one visual loss patient group succeeded at optimal cue combination, whilst the other patient group (patients with central vision loss) did not. We propose that sensory remapping due to changes in fixation behavior may contribute to apparent failures in the latter group.

Keywords

Multisensory combination; audio-visual localization; progressive visual loss; reliability-weighted averaging.

Public Significance Statement

We examined how patients with gradual vision loss combined their deteriorating visual sense with audition (hearing) to localize targets. Humans usually combine different senses optimally, by taking their differing reliabilities into account, but it was not known whether patients with sensory loss would also succeed in this. Patients with gradual central vision loss did not combine visual and auditory estimates of location according to their reliabilities, while patients with gradual peripheral vision loss – and normally sighted adults – did. These results indicate that humans do not always combine sensory estimates optimally following gradual sensory changes. Some patients may have performed sub-optimally because they may have learnt to fixate eccentrically, which could have changed the mapping between locations of visual and auditory targets. The results highlight the need to also consider possible changes to cross-sensory mappings in children and older adults, who have also been found to combine sensory estimates sub-optimally.

Introduction

In daily life we continuously receive complementary information about our environment from multiple senses. These sensory signals often provide 'redundant' information about the same physical property/event. For example, when deciding whether it is safe to cross the road, we can look *and* listen for approaching traffic and thereby make a judgment based on both visual and auditory estimates. Humans can use sensory redundancy to minimize perceptual uncertainty, by taking a reliability-weighted average of each uni-sensory estimate, known as the maximum likelihood estimate (MLE; Ernst, 2006).

A large body of research has found that human adults combine sensory estimates according to this optimal MLE model, (e.g. Alais & Burr, 2004; Ernst & Banks, 2002; Gepshtein & Banks, 2003; Helbig & Ernst, 2007). For example, Alais and Burr (2004) asked human adults to localize briefly-presented visual Gaussian blobs and/or auditory clicks presented in central space (±20°). Results showed that human adults minimized the uncertainty of their bimodal location estimates, indicating that they were combining visual and auditory location estimates optimally. Moreover, as the reliability of the visual cue decreased (when the stimulus was made more blurred), participants increased the weight that they assigned to the auditory information, demonstrating that they were weighting cues according to their relative reliability.

Researchers have shown that adults are able to re-weight signals if their relative reliability changes from one trial to the next (e.g. Alais & Burr, 2004; Ernst & Banks, 2002). However, less is known about how human adults adapt to the gradual changes in sensory reliability that occur during ageing or disease. Children and older adults

have been found to weight cues sub-optimally in multisensory tasks (Bates & Wolbers, 2014; Gori, Del Viva, Sandini, & Burr, 2008; Nardini, Begus, & Mareschal, 2013). For example, in a navigation task, Bates and Wolbers (2014) found that older adults weighted vision less (and non-visual, e.g. vestibular information, more) than predicted by the relative reliabilities of the cues, whereas, consistent with earlier research (Nardini, Jones, Bedford, & Braddick, 2008), younger adults showed optimal cue combination. In development and ageing the reliabilities of different senses are gradually changing. For example, vestibular anatomical changes that occur during aging can gradually impact the reliability of vestibular information for completing certain behavioral tasks (Anson & Jeka, 2015). Consequently, children and older adults may weight sensory information sub-optimally because they have not fully accounted for gradual changes to the reliability of their senses. Given that adults are able to reweight sensory cues from trial to trial, in line with short-term experimental manipulations to the cue reliabilities, (e.g. Alais & Burr, 2004; Ernst & Banks, 2002), why might they fail to account for longer-term changes?

How the nervous system accounts for uncertainty is not yet clear (Ma, Beck, Latham, & Pouget, 2006; Ohshiro, Angelaki, & DeAngelis, 2011), but an interesting possibility raised by the results of studies in children and older adults (Bates & Wolbers, 2014; Gori et al., 2008; Nardini et al., 2013) is that longer-term changes in sensory reliability are dealt with differently to short-term trial-to-trial changes. For example, there could be a general reliability setting for a particular sensory cue (e.g. a visual cue to location; Alais & Burr, 2004) that is immediately modulated by the specific sensory information on a particular trial, but whose overall setting is more difficult to change. However, in development and ageing there is also the possibility

that the cue combination process itself is immature or deficient (e.g. Dekker et al., 2015), and consequently age-related changes in reliability do not offer a clear way to address this question. Here we instead ask how patients who are experiencing gradual loss of a sense (vision) account for this during audio-visual cue combination. Surprisingly, despite considerable recent interest in Bayesian models of cue combination (e.g. Trommershauser, Kording, & Landy, 2011), we know of no other studies to date that have compared cue combination by patients experiencing gradual visual loss with Bayesian predictions.

Retinal degenerative diseases, including retinitis pigmentosa and macular degeneration, lead to progressive visual deterioration that is often, at least initially, limited to certain parts of the visual field. Consequently, in such cases, the nervous system must account for both deteriorations in visual reliability and changes in visual reliability across the visual field. Even in normally sighted adults, the reliability of vision changes across the visual field, with visual precision decreasing as a function of eccentricity due to changes in the density of photoreceptors (Dacey & Petersen, 1992). Previous research has not assessed whether normally sighted human adults weight vision optimally in peripheral (> 20 degrees) as well as central space. However, Charbonneau, Veronneau, Boudrias-Fournier, Lepore, and Collignon (2013) found that the visual capture of spatially misaligned auditory information in human adults declines with eccentricity, suggesting that adults do reduce their reliance on vision in audio-visual peripheral spatial decisions.

Interestingly, auditory localization thresholds also deteriorate with eccentricity, and so individuals with normal sight and hearing show increased localization uncertainty for

auditory (Mills, 1958; Perrott, 1984) and visual stimuli (Perrott, Costantino, & Cisneros, 1993) in peripheral compared to central locations. Consequently, while the relative reliability of visual and auditory cues may change across the visual field (depending on the stimuli to be localized), increased eccentricity generally has a deleterious effect on the reliability of both cues. In individuals with progressive visual loss, the additional central and/or peripheral loss would be expected to change the relative reliabilities of the two senses markedly in comparison to controls. However, changes in the relative reliability of visual and auditory cues may be further complicated by compensatory changes in residual senses. For example, (early and late-onset) blind humans and animals show enhanced auditory target detection (Fieger, Roder, Teder-Salejarvi, Hillyard, & Neville, 2006) and auditory localization (King & Parsons, 1999; Rauschecker & Kniepert, 1994; Voss et al., 2004) on certain tasks. While the effect of partial vision loss on residual senses is less clear, some findings suggest blind individuals with residual vision show changes in non-visual processing too (Cunningham, Weiland, Bao, & Tjan, 2011; Lessard, Pare, Lepore, & Lassonde, 1998).

Here we assessed whether human adults experiencing progressive visual deterioration weight and combine visual and auditory cues to location optimally, i.e. in line with MLE predictions. Normally sighted adults and those diagnosed with a retinal degenerative disease causing primarily either central or peripheral visual loss were asked to localize stimuli using vision alone, hearing alone or both together. Measured visual weights and measured bimodal estimates were compared to MLE predictions. This allowed us to ask: do patients who are losing vision account for any deterioration in visual reliability (i) optimally, in much the same way that normally sighted adults

account for experimental manipulations of visual reliability, or (ii) sub-optimally, as has been observed in younger and older adults experiencing gradual changes to their senses.

Methods

Ethics Statement

Patients were recruited from Moorfields Eye Hospital NHS Foundation Trust, London, UK, and normally sighted adults were recruited through the UCL psychology online subject pool. The study received approval from the London Hampstead research ethics committee. Informed written consent, according to the Tenets of the Declaration of Helsinki, was obtained from all participants prior to participation.

Participants

Participants were twelve adults with central vision loss (7 male, M= 49.2 yrs, SD = 11.5 yrs), ten adults with peripheral vision loss (7 male, M = 40.9 yrs, SD = 10.4 yrs; see Table 1), and twelve age-matched normally sighted adults (6 male, M = 48.5 yrs, SD = 16.0 yrs). Participants were identified as having either primarily central or peripheral vision loss by their clinician (MM), based on their diagnosis, clinical findings and results of investigations (retinal imaging and visual field testing), on attending an appointment at Moorfields Eye Hospital. Most participants with central vision loss (10/12) had been diagnosed with Stargardt Disease (Rotenstreich, Fishman, & Anderson, 2003), whereas most participants with peripheral vision loss (9/10) had been diagnosed with Retinitis Pigmentosa (Hartong, Berson, & Dryja, 2006). Note that participants diagnosed with peripheral vision loss had progressive retinal conditions that affect peripheral vision in the first instance with central visual loss later in the disease process. However, at the time of this study, their peripheral vision was most severely affected, and their central visual fields (up to 18 degrees)

were relatively preserved. Five participants with peripheral vision loss (IDs 06, 07, 08, 09, 10) were not able to complete the auditory-visual localization task in peripheral space (described below), because they were unable to detect the visual targets presented in the periphery. Participants identified as having central vision loss had retinal conditions that affected the cells in their macular (central vision) only (isolated macular dystrophy). All normally sighted adults had visual acuities of between -0.18 and 0.16 logMAR (Snellen equivalent of between 6/4 and 6/9), as assessed using a logMAR letter chart. A logMAR score of 0 (Snellen equivalent of 6/6) indicates that the observer can resolve details as small as 1 minute of visual angle. A logMAR score of 0.3 (Snellen equivalent of 6/12) indicates that the observer can resolve details as small as 2 minutes of visual angle. All participants reported having normal hearing.

Apparatus & Stimuli

Stimuli were presented using 122 light-emitting diode pixels (Adafruit 12mm diffused flat digital RGB LED pixels; see Jones, Garcia, & Nardini, 2015) and 9 speakers (50mm x 90mm Visaton speaker SC 5.9), mounted on a 2.5m semi-circular ring (circle radius: 2.87m), spanning -15 to +30 degrees (see Fig. 1). A further 2 light-emitting diode pixels (LEDs) and 1 speaker were mounted on the wall, 20 degrees left of the ring, and served as the fixation target during peripheral stimuli presentation. Stimulus presentation was controlled using Matlab (Version R2014a, The MathWorks Inc., Natick, Massachusetts, United States) and the Psychophysics toolbox extensions (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007; Pelli, 1997), on a Windows 7 computer. An Arduino Uno microcontroller (SmartProjects, Strambino, Italy) was used to interface between the control computer and the LED pixels. The Matlab

PsychPortAudio ASIO interface controlled audio presentation via a Focusrite Saffire PRO 40 sound card and audio signals were amplified using Lypin Hi-Fi 2.1 stereo amps. The sampling rate was 44.1kHz and speakers were equalized for intensity using a sound level meter.

Table 1: Details of all Participants with Central or Peripheral Vision Loss.

Snellen visual acuity is reported. In the Snellen fraction, the numerator represents the distance at which the participant would need to approach to read letters that an observer with normal acuity could read from the distance reported in the denominator. Hence, a participant with 6/12 acuity would need to approach a distance of 6m to read letters that an observer with normal acuity could read at 12m.

***Participants with peripheral vision loss who were not able to complete the auditory-visual localization task in peripheral space.**

ID	Visual Disease	Gender	Age	Visual Acuity	
				Right	Left
01	Stargardt disease	F	59	2/60	3/60
02	Stargardt disease	F	39	6/60	6/12
03	Stargardt disease	F	51	6/5	6/5
04	Macular dystrophy	M	51	6/18	6/9
05	Stargardt disease	M	50	1/60	1/24
06	Stargardt disease	M	62	6/5	6/18
07	Stargardt disease	F	51	6/36	6/36
08	Stargardt disease	F	59	6/5	6/5
09	Stargardt disease	M	60	3/60	6/5
10	Stargardt disease	M	43	6/60	6/36
11	Macular dystrophy	M	21	6/36	6/36
12	Stargardt disease	M	44	6/5	6/6
01	Retinitis pigmentosa	M	48	6/9	6/12
02	Retinitis pigmentosa	F	41	6/60	6/36
03	Retinitis pigmentosa	M	28	6/5	6/5

04	Retinitis pigmentosa	M	32	6/9	6/12
05	Rod Cone Dystrophy	M	40	6/12	6/9
06*	Retinitis pigmentosa	F	55	4/60	6/9
07*	Retinitis pigmentosa	F	35	6/5	6/6
08*	Retinitis pigmentosa	M	35	6/5	6/5
09*	Retinitis pigmentosa	M	60	6/9	6/24
10*	Retinitis pigmentosa	M	35	6/12	6/9

Figure 1: The Ring of LEDs and Speakers. On each presentation a flash of lights from a subset of LEDs (outlined in purple) and/or a noise from a speaker (outlined in blue) was presented. Participants maintained their head position fixed at straight ahead, using a chin rest (outlined in red), and entered responses using the keyboard (outlined in green).

All 122 LEDs were powered to show white light (2223 cd/m^2) constantly throughout the duration of the experiment. The visual stimulus was a 25 msec flash of white light from 50 adjacent LEDs, (spaced 0.5° apart, spanning 25°). The luminance of the visual stimulus was increased for peripheral (3055 cd/m^2) compared to central (2639 cd/m^2) space, to account for the approximate doubling of Differential Luminance Sensitivity (DLS) from 36° to 1° (Brenton & Phelps, 1986). The luminance of the visual stimulus was also increased for participants with vision loss, where necessary, to increase the reliability of the visual stimulus. This was assessed using a short practice task of 32 trials (described below). Where a participant was unable to discriminate between the standard and the comparison stimuli at the largest

discrimination distances (13° & 18°), the luminance of the visual stimulus was increased, and the practice task was repeated. Audio stimuli were 100 msec (25 ms rise and 25 ms fall time) band-pass-filtered noise bursts (tenth octave centered on 1000Hz) presented at 50 dB SPL (± 1 dB), presented against a continuously played background pink noise presented at 20 dB SPL. Note that in an attempt to more closely match visual and auditory cue reliability for location, the visual stimulus duration (25ms) was shorter than the auditory stimulus duration (100ms).

Procedure

Participants were asked to localize visual (light flash) and auditory (noise burst) stimuli presented separately or together, in a dimly lit, quiet room. Each trial began with the presentation of a fixation cue at 0 degrees (i.e. straight ahead), consisting of a red 400 msec light flash from two LEDs (13600 cd/m^2) and a simultaneous 400 msec 500 Hz (50 dB SPL) tone played from the corresponding speaker. Participants were asked to maintain their eye gaze in this direction throughout the whole experiment, and a chin-rest (with forehead-rest) was used to fix their head position. They were instructed to maintain both eyes open throughout the experiment (including during the audio-only trials), and to maintain their head as still as possible. All participants appeared to comply. Following the fixation cue, two sets of stimuli were presented successively: a standard (central: 1°, peripheral: 36°, right of fixation) and one of eight comparison stimuli (0-17° right of the standard). The order of the standard and comparison presentation was counterbalanced. The commencement of the second stimulus succeeded that of the first by 500ms. Participants were asked to press a key to indicate whether the first or second stimulus was further to the right. A stimulus consisted of a flash of light, a noise burst, or both together, and the type of stimulus varied between blocks. For example, during a visual-localization block, participants

were asked: “Was the first flash or the second flash further to your right? Press ‘1’ if first, ‘2’ if second”.

Blocks consisted of audio-only, vision-only or bimodal (audio-visual) stimuli. Where visual and auditory stimuli were presented together, stimuli were either presented in congruent locations (no-conflict), or the visual stimulus was displaced leftward (central: by 3°, peripheral: by 4°) compared to the auditory stimulus (conflict). The conflict trials were used to measure cue weighting.

The experiment was divided into two parts, one part consisting of localization in central space (central condition), the other of localization in peripheral space (peripheral condition). The order of these was counterbalanced (by the experimenter) across participants. Note that the set-up in central and peripheral conditions was exactly the same, except that participants were rotated leftwards by 35 degrees in the peripheral condition.

Prior to commencing the test blocks for central and peripheral tasks, participants completed two practice blocks, one with each of the unimodal stimuli used in the experiment. During testing, they completed 24 test blocks (6 audio-only, 6 vision-only, 12 audio-visual) of 64 trials, at each location (central and peripheral). Each block included 8 trials at each of the following comparison angles: 1°, 2°, 3°, 4°, 6°, 9°, 13°, and 18°. Equal numbers of conflict and no-conflict trials were randomly interleaved within audio-visual blocks. Thus, there were equal numbers of trials that were audio-only, visual-only, audio-visual (consistent) and audio-visual (conflict).

There were 48 trials per comparison distance for each of these conditions (see Table 2).

On average, the experiment took five hours in total to complete. At the end of each experimental block, participants were required to press a button to commence the next block, or had the option to take a break if needed. Hence, participants were able to take breaks frequently, as and when needed. They were asked to take at least two breaks during both the central and peripheral tasks, and a break of at least 30 minutes, between these tasks.

Table 2: Experimental Tasks, Blocks and Trials.

Task	**Blocks (random block order)**	**Trials (random trial order)**
Practice	1 AUDIO only	32 trials/block (4 trials/location)
	1 VISION only	32 trials/block (4 trials/location)
Test 1: Central/Peripheral (24 blocks)	6 AUDIO only	64 trials/block (8 trials/location)
	6 VISION only	64 trials/block (8 trials/location)
	12 AUDIO-VISUAL	32 non-conflict & 32 conflict trials/block (8 trials/location)
Test 2: Peripheral/Central (24 blocks)	6 AUDIO only	64 trials/block (8 trials/location)
	6 VISION only	64 trials/block (8 trials/location)
	12 AUDIO-VISUAL	32 non-conflict & 32 conflict trials/block (8 trials/location)

Data Analysis

The proportion of trials in which the second stimulus was perceived as being to the right of the first was plotted against the size of the displacement between the two stimuli, for each cue (audio-only, vision-only, audio and vision: no conflict and conflict), and for each location (central, peripheral). Data were fitted with cumulative Gaussian functions, using psignifit toolbox version 2.5.6 for Matlab (see http://bootstrap-software.org/psignifit/), a software package which implements the maximum-likelihood method described by Wichmann and Hill (2001a). The standard deviation (σ) and the mean (μ) of each function provided, respectively, estimates of the cue's reliability and point of subjective equality (PSE). Hence, the standard deviation of each function provides a measure of the cue's uncertainty (which is inversely proportional to the cue's reliability). Functions were fitted to each individual participant's data (see Fig. 2).

The maximum likelihood estimate is given by the mean of the single cue estimates, $\hat{s}_{AV}$, weighted by their respective reliabilities:

$$\hat{s}_{AV} = w_v \hat{s}_v + w_A \hat{s}_A \qquad (1)$$

where $\hat{s}_v$ is the visual estimate, $\hat{s}_A$ is the auditory estimate, and w_V and w_A are the optimal relative weights for each modality, inversely proportional to their variances, (σ^2):

$$w_V = \frac{1/\sigma_V^2}{1/\sigma_V^2 + 1/\sigma_A^2} = \frac{\sigma_A^2}{\sigma_V^2 + \sigma_A^2} \quad (2)$$

$$w_A = \frac{1/\sigma_A^2}{1/\sigma_A^2 + 1/\sigma_V^2} = \frac{\sigma_V^2}{\sigma_A^2 + \sigma_V^2} \quad (3)$$

Thus the maximum likelihood estimate (MLE) produces a final estimate with the lowest possible variance (i.e. uncertainty):

$$\sigma_{AV} = \frac{\sigma_A^2 \sigma_V^2}{\sigma_A^2 + \sigma_V^2}, \ where \ \sigma_{AV} \leq min\left(\sigma_A^2, \sigma_V^2\right) \quad (4)$$

For each participant, measured unimodal reliabilities (σ) were used to compute the MLE prediction, and their measured bimodal reliability was compared to this prediction.

The PSE describes the point at which participants were equally likely to perceive the comparison stimulus as left or right of the standard. To assess whether participants weighted cues optimally during their localization estimates, no-conflict and conflict PSEs were used to compute the actual weighting given to vision in bimodal trials (Eq. 4), and this was compared with the predicted optimal visual weight (Eq. 2).

$$\hat{w}_V = \frac{PSE_{Conflict} - PSE_{No\ Conflict}}{Visual\ Displacement} \quad (4)$$

Thus, a difference in conflict and no conflict PSEs equal to the size of the visual displacement would indicate that participants relied entirely on visual information in their bimodal localization judgments, whereas no difference in PSEs would indicate that participants relied entirely on auditory information (see Results, Fig. 2, for an example participant's data).

Paired sample *t*-tests were used to test for differences in uncertainty between bimodal and unimodal conditions, and for differences in predicted and measured visual weights between central and peripheral space. Linear regression analyses were used to assess whether there were significant relationships between measured and predicted reliabilities, and measured and predicted visual weights. A repeated measures ANOVA with location (central, peripheral) as the within-subjects factor and participant group (normally sighted, central vision loss, peripheral vision loss) as the between subjects factor was used to compare cue uncertainty across participant groups.

Results

Five participants with peripheral vision loss did not complete the peripheral condition, as they were unable to perceive the visual targets presented in peripheral space. Therefore, the results of all ten participants with peripheral vision loss in the central localization task, but the results of just five participants in the peripheral localization task, are reported here. Figure 2 plots data points and fitted psychometric functions from a representative normally sighted participant and a representative participant with central vision loss in the central localization task.

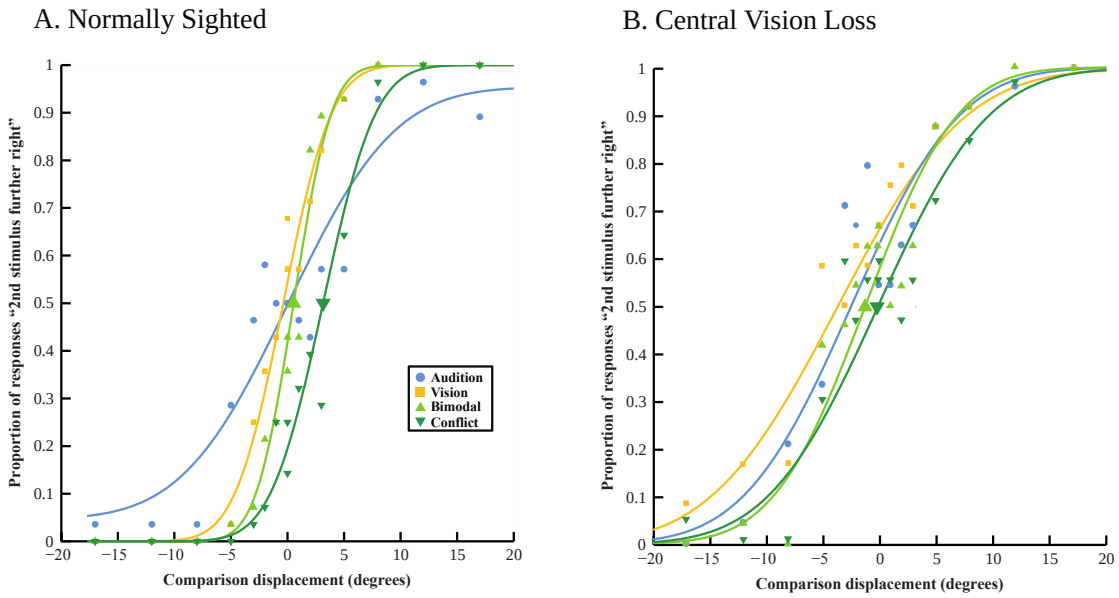

Figure 2: Data from a representative Normally Sighted Participant (A) and Participant with Central Vision Loss (B), in the Central Localization Task. For the normally sighted participant, localization with Vision alone was more reliable than with Audition alone, reflected by the steeper slope of the psychometric curve (and thus lower σ). Larger marker points indicate points of subjective equality (PSEs) for the Bimodal (no conflict) and Conflict conditions. In the Conflict condition, the comparison visual stimulus was displaced leftward by 3 degrees. This conflict shifted the participant's psychometric function rightward by 2.6°. From this we conclude that this participant relied relatively more on vision than on audition during bimodal conditions, with an estimated vision weight of 0.87 (w_V = 2.6/3 = 0.87). Note that in the experiment, all comparison stimuli in no-conflict conditions were right of the standard stimulus. The negative numbers on the x-axis reflect trials in which the comparison stimulus was presented first.

Uncertainty

We first analyzed standard deviations (σ) of fitted functions, a measure of uncertainty – higher values of σ indicate greater uncertainty (lower reliability) of perceptual estimates. Figure 3 plots mean uncertainty for the single cue (Audition, Vision) and Bimodal conditions, and Predicted (ideal observer, MLE) uncertainty, for each group, in central and peripheral conditions. Table 3 reports the results of paired t-test

comparisons of Bimodal uncertainty with (i) each single cue; (ii) the best single cue; and (iii) ideal observer (MLE) predictions.

Comparison with (i) each single cue tests whether, on average, a group showed reduced uncertainty given both cues together (Bimodal) vs. either cue alone. The comparison with (ii) the best single cue selects, for each participant, the single cue (Vision or Audition) with the lower uncertainty and compares this with Bimodal performance. This most directly tests whether participants reduced their uncertainty in Bimodal conditions relative to the best single cue, but is also a conservative test. Always selecting the unimodal cue with the lowest uncertainty can lead to a systematic bias to select cues with lower estimated uncertainty than their true uncertainty (due to measurement noise). The comparison with (iii) ideal observer (MLE) predictions tests whether Bimodal uncertainty deviates significantly from MLE predictions. In sub-optimal cue combination, Bimodal uncertainty would be expected to be higher than predicted by the MLE.

Figure 4A-B and Table 4 report the results of regression analyses testing whether MLE Predictions predict the Bimodal uncertainties of individual participants. Findings of significant relationships were followed up with tests of whether regression slopes differed significantly from optimal (unity).

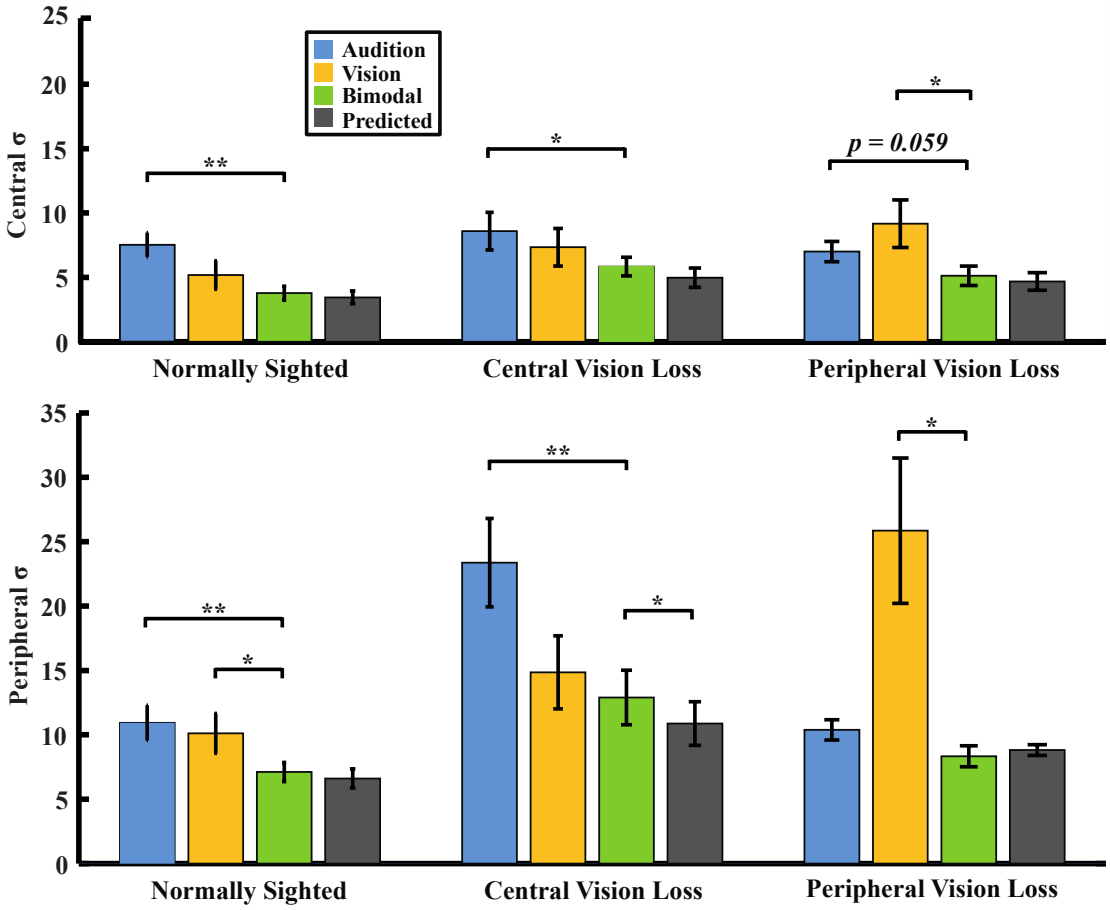

Figure 3: Measured and Predicted Uncertainty for Visual-Auditory Localization.

Visual, Auditory, Bimodal and Predicted localization uncertainty, in central (upper panel) and peripheral (lower panel) space, for participants with Normal Sight, Ccntral Vision Loss or Peripheral Vision Loss. Error bars show the standard error of the mean, (note that this is different to the standard error of the difference, compared in paired t-tests). Bimodal uncertainty was compared with each single cue's uncertainty, and also with the ideal (MLE) prediction. (* indicates $p < .05$; ** indicates $p < .01$).

Table 3: Results of Paired Sample t-tests comparing Bimodal uncertainty (σ) with (i) Unimodal (Vision, Audition) uncertainty; (ii) uncertainty of each participants' Best Unimodal Cue (Vision or Audition); (iii) MLE Prediction (* indicates $p < .05$; ** indicates $p < .01$).

		Normally Sighted	Central Vision Loss	Peripheral Vision Loss
Central	Vision	$t_{[11]} = 1.85$, $p = 0.091$	$t_{[11]} = 1.29$, $p = 0.225$	$t_{[9]} = 2.85$, $p = 0.019$ *
	Audition	$t_{[11]} = 3.21$, $p = 0.008$ **	$t_{[11]} = 2.49$, $p = 0.030$ *	$t_{[9]} = 2.17$, $p = 0.059$
	Best unimodal cue	$t_{[11]} = 1.60$, $p = 0.138$	$t_{[11]} = 0.35$, $p = 0.731$	$t_{[9]} = 0.57$, $p = 0.582$
	Prediction	$t_{[11]} = 1.82$, $p = 0.096$	$t_{[11]} = 2.01$, $p = 0.070$	$t_{[9]} = 0.94$, $p = 0.371$
Peripheral	Vision	$t_{[11]} = 2.25$, $p = 0.046$ *	$t_{[11]} = 0.80$, $p = 0.438$	$t_{[4]} = 3.44$, $p = 0.026$ *
	Audition	$t_{[11]} = 3.29$, $p = 0.007$ **	$t_{[11]} = 4.69$, $p < 0.001$ **	$t_{[4]} = 1.31$, $p = 0.261$
	Best unimodal cue	$t_{[11]} = 1.44$, $p = 0.178$	$t_{[11]} = 0.40$, $p = 0.695$	$t_{[4]} = 1.41$, $p = 0.231$
	Prediction	$t_{[11]} = 0.95$, $p = 0.361$	$t_{[11]} = 2.61$, $p = 0.024$ *	$t_{[4]} = 0.67$, $p = 0.538$

Central Localization

All three participant groups in the central localization task (Fig. 3, top) showed lower mean uncertainty for bimodal relative to unisensory judgments, although bimodal uncertainty was not (i) significantly lower than that for either single cue, or (ii) significantly lower than the best single cue (see Table 3). For all three groups, bimodal central localization uncertainty was (iii) not significantly different to MLE predictions (see Table 3).

Regression analyses of individual participants' bimodal uncertainties as compared with their individual MLE predictions (Fig. 4A & Table 4) show that the MLE model significantly predicted individual participants' bimodal reliabilities in all three groups. Furthermore, the slope of the regression line for predicted versus measured reliabilities did not significantly deviate from optimal (unity) for any group (see Table 4).

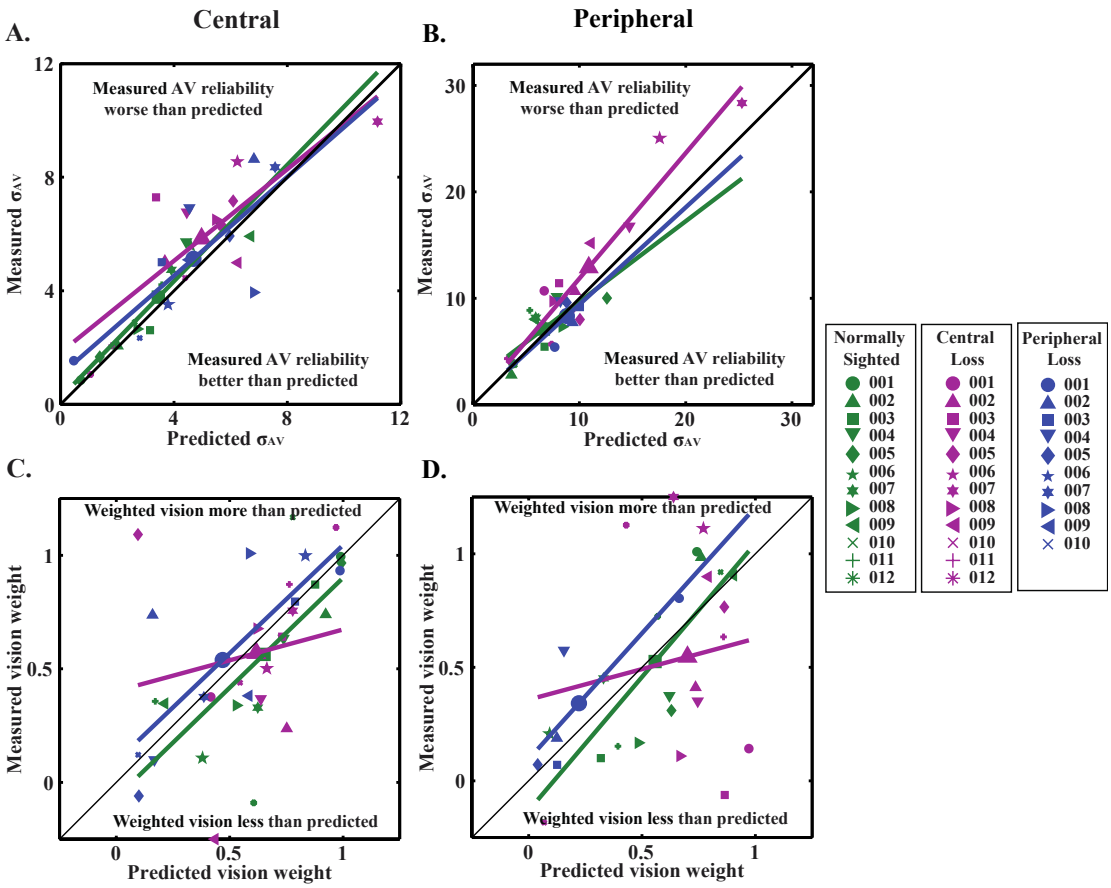

Figure 4: Top Panel - Predicted and measured audio-visual (AV) reliabilities in central (A) and peripheral (B) space. Lower Panel - Predicted and measured vision weights in central (C) and peripheral (D) space. Group means depicted by larger symbols.

Table 4: Results of Linear Regression Analyses comparing Predicted and Measured Reliabilities and Vision Weights, (* indicates $p < .05$; ** indicates $p < .01$). Where the relationship between predictions and measurements was significant, t-tests were used to assess whether this relationship deviated significantly from optimal (unity).

		Normally Sighted	Central Vision Loss	Peripheral Vision Loss
Central	Reliabilities	$F_{[2,10]} = 83.7$, $p < 0.01$ **	$F_{[2,10]} = 22.0$, $p < 0.01$ **	$F_{[2,8]} = 13.6$, $p < 0.01$ **
		$R^2 = 0.89$, $\beta_1 = 1.03$	$R^2 = 0.69$, $\beta_1 = 0.81$	$R^2 = 0.63$, $\beta_1 = 0.87$
	Optimal	$t_{[10]} = 0.273$, $p = 0.79$	$t_{[10]} = 1.18$, $p = 0.27$	$t_{[8]} = 0.542$, $p = 0.60$
	Weights	$F_{[2,10]} = 9.98$, $p = 0.01$ *	$F_{[2,10]} = 0.26$, $p = 0.62$	$F_{[2,8]} = 12.9$, $p < 0.01$ **
		$R^2 = 0.50$, $\beta_1 = 0.97$	$R^2 = 0.03$, $\beta_1 = 0.27$	$R^2 = 0.62$, $\beta_1 = 0.95$
	Optimal	$t_{[10]} = 0.097$, $p = 0.92$		$t_{[8]} = 0.185$, $p = 0.86$
Peripheral	Reliabilities	$F_{[2,10]} = 13.0$, $p < 0.01$ **	$F_{[2,10]} = 78.6$, $p < 0.01$ **	$F_{[2,3]} = 0.84$, $p = 0.43$
		$R^2 = 0.57$, $\beta_1 = 0.76$	$R^2 = 0.89$, $\beta_1 = 1.18$	$R^2 = 0.22$, $\beta_1 = 0.91$
	Optimal	$t_{[10]} = 1.143$, $p = 0.28$	$t_{[10]} = 1.385$, $p = 0.20$	
	Weights	$F_{[2,10]} = 17.3$, $p < 0.01$ **	$F_{[2,10]} = 0.18$, $p = 0.68$	$F_{[2,3]} = 7.22$, $p = 0.08$
		$R^2 = 0.63$, $\beta_1 = 1.18$	$R^2 = 0.02$, $\beta_1 = 0.27$	$R^2 = 0.71$, $\beta_1 = 1.11$
	Optimal	$t_{[10]} = 0.643$, $p = 0.53$		

Peripheral Localization

As with central localization, in peripheral space (Fig. 3, bottom row) all three participant groups showed lower mean uncertainty for bimodal relative to unisensory judgments. For normally sighted participants, on average mean bimodal localization uncertainty was (i) significantly lower than either vision or audition alone (see Table 3). However, when (ii) selecting the best single cue for each participant and comparing this with bimodal localization uncertainty, there is no significant difference (Table 3). Comparisons of (iii) bimodal and predicted (MLE) uncertainty showed a significant difference for one group – participants with central vision loss – whose bimodal uncertainty was significantly higher than predicted (see Fig. 3, bottom row, middle, & Table 3).

As in the Central task, there was a significant linear relationship between predicted and measured reliabilities (see Fig. 4B & Table 4), and this relationship did not significantly deviate from optimal (see Table 4). Note that while the slope of the regression line for the Central Vision Loss group did not differ from optimal (Fig. 4B & Table 4), bimodal uncertainty was systematically higher than predicted (Fig. 3, bottom row, middle, & Table 3), as also seen in the shift of this regression line upwards from the unity (optimal) line in Figure 4.

Overall, participants tended to reduce the uncertainty of bimodal estimates relative to unimodal cues (Fig. 3), although the comparisons did not reach statistical significance. Despite this, bimodal uncertainty tended to be well predicted by the MLE (Fig. 4A-B), and tended not to deviate significantly from optimal MLE predictions (either overall, Fig. 3, or on an individual basis; comparison with unity in

Table 4). The notable exception was the group of participants with central vision loss, who had significantly higher bimodal uncertainty than predicted in peripheral space (Fig. 3, bottom row, middle, & Table 3).

Cue weighting

Next, we analyzed cue weighting. Figure 4C-D plots individual measured vision weights against individual optimal (MLE) visual weight predictions at central (Fig. 4C) and peripheral (Fig. 4D) locations.

Central Localization

For normally sighted adults and participants with peripheral vision loss, there was a significant linear relationship between measured and predicted vision weights in central space ($p <= 0.01$; see Table 4, Fig. 4C). One-way t-tests indicated that the slope of the regression line for these linear relationships did not significantly deviate from optimal (Table 4). In contrast, for participants with central vision loss, there was no significant relationship between measured and predicted vision weights ($p = 0.62$; see Table 4, Fig. 4C).

Peripheral Localization

As in central space, for normally sighted adults, there was a significant linear relationship between measured and predicted vision weights in peripheral space ($p <= 0.01$; see Table 4, Fig. 4D), which again did not deviate significantly from optimal (Table 4). Participants with peripheral vision loss showed a similar relationship between measured and predicted vision weights ($p = 0.075$), but this was not statistically significant, very likely due to the small sample size ($n = 5$). However, as in central space, for participants with central vision loss there was no significant

relationship between measured and predicted visual weights ($p = 0.68$; see Table 5, Fig. 3D).

Overall, the results indicate that for normally sighted participants and participants with peripheral vision loss (excluding peripheral space, where $n = 5$), there was a significant relationship between predicted and measured vision weights, with measured vision weights not deviating significantly from optimal MLE predictions. However, for participants with central vision loss, there was no relationship between predicted and measured vision weights. This indicates that this group did not take cue reliabilities into account during cue combination, which could also explain their significantly higher-than-predicted uncertainty in the Bimodal condition (Fig. 3, bottom row, middle).

Central versus Peripheral Localization

Table 5 lists mean measured and predicted vision weights, for central and peripheral tasks, for each group. Table 6 presents the results of paired sample *t*-tests comparing these weights across Central and Peripheral conditions. We expected that performing the task in the periphery as compared with the center would alter the relative reliabilities of vision and audition and so call for re-weighting. However, differences in *predicted* visual weights between central and peripheral space were not significant for any group (Table 6). As we did not see statistically significant reweighting predicted even for ideal observers in this experiment, it is perhaps not surprising that we also did not see significant differences in *measured* central versus peripheral vision weights either (Table 6).

Table 5: Mean (SE) Measured and Predicted Vision Weights for each Participant Group

		Normally Sighted	Central Vision Loss	Peripheral Vision Loss
Central	Measured	0.56 (0.11)	0.57 (0.11)	0.54 (0.13)
	Predicted	0.65 (0.08)	0.62 (0.06)	0.47 (0.11)
Peripheral	Measured	0.53 (0.10)	0.55 (0.14)	0.34 (0.15)
	Predicted	0.56 (0.07)	0.70 (0.07)	0.22 (0.11)

Table 6: Results of Paired Sample t-tests comparing Predicted and Measured Vision Weights between Central and Peripheral Space.

	Normally Sighted	Central Vision Loss	Peripheral Vision Loss
Predicted	$t_{[11]} = 1.02$, $p = 0.33$	$t_{[11]} = 0.77$, $p = 0.46$	$t_{[4]} = 1.76$, $p = 0.15$
Measured	$t_{[11]} = 0.29$, $p = 0.78$	$t_{[11]} = 0.15$, $p = 0.89$	$t_{[4]} = 0.73$, $p = 0.51$

Comparison of Auditory Thresholds

A repeated measures ANOVA with location (central, peripheral) as the within-subjects factor, and participant group (normally sighted, central vision loss, peripheral vision loss) as the between-subjects factor showed a significant effect of location on auditory uncertainty ($F_{[1,26]} = 30.8$, $p < 0.001$), with greater uncertainty in the periphery. Furthermore, there was a significant interaction between group and location on auditory uncertainty ($F_{[2,26]} = 9.76$, $p = 0.001$). As Figure 3 shows, this is driven by the unusually high auditory uncertainty of participants with central vision loss in the periphery. Post-hoc t-tests (p values for multiple comparisons adjusted using a Bonferonni correction) showed that participants with central vision loss showed significantly higher auditory localization uncertainty relative to normally sighted controls ($t_{[22]} = 3.37$, $p = 0.008$), but not participants with peripheral vision loss ($t_{[15]} = 2.39$, $p = 0.12$; but note the small sample size, n = 5). No differences in auditory localization in central space between participants with central vision loss and other participants were found (normally sighted controls: $t_{[22]} = 0.61$, $p = 0.55$; participants with peripheral vision loss: $t_{[20]} = 0.90$, $p = 0.38$). These results indicate that participants with central vision loss had to account not only for their loss of vision, as we expected, but also for a loss in auditory localization ability.

Summary

In both central and peripheral space, both controls and patients with peripheral vision loss showed bimodal uncertainty that did not significantly differ from optimal MLE predictions (Fig. 3 & 4). Although bimodal uncertainty was not significantly reduced relative to the best single cue, individual participants' bimodal uncertainties were well

predicted by their individual MLEs (Fig. 4A-B), as were individual cue weights (Fig. 4C-D). Participants with central vision loss showed a different pattern of results: these participants showed significantly higher bimodal uncertainty than predicted in peripheral space (Fig. 3), and their measured vision weights did not match predictions based on individual cue reliability (Fig. 4C-D). This group's non-optimal weighting (Fig. 4C-D) may explain their higher-than-predicted bimodal uncertainty (Fig. 3). Interestingly, this group also showed unexpectedly high auditory uncertainty in the periphery, indicating that they needed to account not only for their vision loss but also a loss in auditory localization ability. Finally, localization of the stimuli used did not require (or show) significant re-weighting by individuals across central versus peripheral space.

Discussion

This study aimed to understand whether adults diagnosed with progressive visual loss are able to account for the long-term changes to the reliability of their vision. Results showed that normally sighted adults combined visual and auditory location cues optimally in both central and peripheral space, by weighting cues according to their relative reliability. Similarly, patients with visual loss that primarily affected their peripheral vision also weighted visual and auditory cue to location according to their reliability, in line with optimal MLE predictions. In contrast, patients with central vision loss did not weight vision optimally in either central or peripheral space; measured vision weights showed no relation to predictions. These results suggest that human adults are able to combine multisensory cues in a way that compensates for some types of long-term progressive sensory changes, but not others.

Previous studies have shown that normally sighted adults can rapidly re-weight sensory cues as their relative reliability is manipulated from trial to trial (e.g. Alais & Burr, 2004; Ernst & Banks, 2002). Here we found that adults experiencing progressive peripheral vision loss weighted vision in line with MLE predictions (at least in central space, since results for peripheral space are limited by sample number), as did normally sighted adults. This suggests that, in addition to short-term manipulations of cue reliability, the nervous system can also account for some longer-term changes to sensory reliability following sensory loss.

However, participants with central vision loss only showed a markedly different pattern of results, in that they did not weight visual and auditory information about

location according to reliability. This group did not show a systematic tendency to either over-weight or under-weight the visual cue. Instead, participants' measured visual weights showed no relationship with optimal reliability-based predictions. Despite this, bimodal localization estimates did not show significantly higher uncertainty compared to the most reliable unisensory cue. Such a result could be explained by complete reliance on the best unisensory cue. However, measured weights did not show a complete reliance on either vision or audition. Hence, the findings suggest that participants with central vision loss combined visual and auditory information, but using sub-optimal weights i.e. weights that did not properly account for each individual's relative cue reliabilities.

Overall, the results show two patient groups with progressive sensory loss, one succeeding and one failing at combining cues according to the MLE rule. Why might the group with central loss, in particular, have failed to weight cues by reliability? An interesting result is that this group also showed strikingly elevated *auditory* localization uncertainty in the periphery, (see similar finding in congenitally blind adults with residual vision by Lessard et al., 1998). It was anticipated that differences across groups would reflect changes to one sense (vision), and that the task for patients, in terms of cue combination, would be to account for progressive changes in this one sense. Instead, the results suggest that the central group had to contend with changes to two senses – potentially a more challenging task for maintaining optimal cue weights than a change only to one sense. This increased difficulty of dealing with changes in both senses could have contributed to this group's difficulties with maintaining correct cue weighting.

We had not expected differences in auditory localization between these different participant groups. Consequently, one possibility is that the impaired auditory localization of participants with central vision loss is linked in some way to the deterioration of their vision. Future research is needed to address whether this is the case. However, irrespective of why participants with central vision loss showed greater auditory localization uncertainty, the question remains as to why they did not account for the relative reliability of their vision and audition when combining these cues.

It is frequently reported that participants with central vision loss learn to rely on eccentric viewing, developing a preferred retinal locus (PRL) that avoids the area of central vision loss (Crossland, Engel, & Legge, 2011). Accordingly, the central vision loss patients may have been learning a different correspondence between the auditory, head-centered, spatial map and the visual, eye-centered, representation of space, (as has been demonstrated in animals following a misalignment of visual-auditory cues, e.g. Feldman & Knudsen, 1997; Wallace & Stein, 2007). Patients in the process of learning this new mapping may have perceived a discrepancy in the spatial location of the target via vision versus audition, at least at some of the comparison positions. They may have fixated the required visual targets centrally, which would change the audio-visual mapping from a usual mapping they may have been learning to use during eccentric fixation. Alternatively, they may have fixated the targets eccentrically, but have still been in the process of learning a new audio-visual mapping for eccentric fixation. All participants were asked to keep their head as still as possible (using the chin and forehead rest provided) and to maintain their eye gaze in the direction of the fixation cue throughout the whole experiment.

However, eye movements were not systematically monitored. Therefore, another possibility is that this patient group found it particularly difficult to maintain fixation. It would be useful to monitor fixation to differentiate between these possibilities in the future. Nevertheless, either way, on some trials, some patients may not have combined cues in line with reliability-based MLE predictions due to a perceived spatial disparity following changes to their fixation.

Ideal observer models have been developed for tasks in which cues are systematically biased and/or spatially inconsistent (e.g. Burge, Ernst, & Banks, 2008; Körding et al., 2007), however the present study did not measure subjective biases or discrepancies across visual versus auditory cues. We propose that subjective misalignment of cues due to changes in fixation behavior could contribute to apparent failures of cue combination in the central vision loss group, but further research is needed to test this interpretation directly. The perceptual uncertainty we measured may be a combination of uncertainty and of effects due to cues sometimes being perceived as systematically biased or not coming from the same source. This would add noise to measures of uncertainty and of cue weighting, and to measures of optimally predicted cue weighting, which depends on measured uncertainty.

In the main experiment, all participant groups showed visual and auditory discrimination thresholds that deteriorated from central to peripheral space. However, the relative reliability of both cues did not change significantly; participants did not have to adjust their relative reliance on visual versus auditory cues between central and peripheral locations and, accordingly, participants showed similar cue weighting across locations. Consequently, it is not clear whether patients with progressive

visual loss account for differences in the relative reliability of visual and auditory cues across their visual field. Follow-up tests using different stimuli that are better suited to finding such differences are needed to establish this.

In summary, the results indicate that when combining visual and auditory cues to location, human adults are able to account for long-term progressive changes to their visual reliability – just as normally sighted adults account for experimental manipulations to visual reliability. However, certain long-term changes to visual reliability that affect the mapping between visual and non-visual cues may be more difficult to account for. We found that participants with central vision loss did not weight visual information in line with MLE predictions based on cue reliability. Importantly, for this group, the progressive visual change appeared to influence both the reliability of vision and audition. We propose that changes in the spatial correspondence between audition and vision, due to the development of eccentric fixation strategies, may have led to subjective perceptual mismatches between vision and audition. Whether such mismatches are present – and whether they are dealt with in line with ideal observer principles (e.g. Burge et al., 2008; Körding et al., 2007) – are questions for future research. It is possible that developing eccentric fixation to deal with central vision loss may come at the (possibly temporary) cost to combining visual and auditory cues for localization. If so, this has interesting implications for the treatment and rehabilitation of adults experiencing visual loss. Low vision rehabilitation services that teach patients to shift their visual field from straight ahead to a peripheral retinal area may want to consider that the accuracy and reliability of non-visual senses could be affected. It may be that patients will gradually learn to correct any misalignments or biases in visual and non-visual spatial information that

result from relying on peripheral vision to fixate centrally. However, training programs in eccentric viewing that include a multisensory component may be beneficial in facilitating such learning.

Can humans account for progressive visual loss in line with MLE principles during multisensory cue combination? To our knowledge, we describe here the first data to address this question. We found one patient group that followed MLE principles, and one that did not. We suggest that the latter group may have experienced changes to cross-modal mapping not captured by the basic MLE model. If so, then it is possible in theory that the latter group's behavior would also be near-optimal, if issues due to remapping could be taken into account – although the measures we collected do not allow us to test that here. This interpretation suggests that in most cases of sensory loss, humans should be able to account for changes in the relative reliability of vision in line with MLE principles; however, further studies with other groups and modalities are clearly needed, including groups experiencing more gradual changes via normal ageing (e.g. Bates & Wolbers, 2014). The results highlight the need to consider possible changes in cross-modal mapping, as well as in unimodal reliability, following sensory loss.

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