Cerebellar degeneration increases visual influence on dynamic estimates of verticality

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Summary

Our perception of verticality relies on combining sensory information from multiple sources. Neuronal recordings in animals implicate the cerebellum in the process, yet disease of the human cerebellum was not found to affect this perception. Here we show that a perceptual disturbance of verticality is indeed present in people with a genetically determined and pure form of cerebellar degeneration (SCA6), but is only revealed under dynamic visual conditions. Participants were required to continuously orient a visually-displayed bar to vertical while the bar-angle was perturbed by a low-frequency random signal, and a random dot pattern rotated in their visual periphery. The random dot pattern was rotated at one of two velocities (4 °/s and 16 °/s), travelling with either coherent or noisy motion. Perceived vertical was biased by visual rotation in healthy participants, particularly in a more elderly group, but SCA6 participants were biased more than both groups. The bias was reduced by visual noise, but more so for SCA6 participants than young controls. Distortion of verticality by visual rotation stems from the stimulus creating an illusion of self-rotation. We modelled this process using a maximum likelihood sensory cue combination model operating on noisy visual and vestibular rotation signals. The observed effects of visual rotation and visual noise could be compellingly explained by cerebellar degeneration, and to a lesser extent ageing, causing an increase in central vestibular noise. This is consistent with the human cerebellum operating on dynamic vestibular signals to inform the process that estimates which way is up.

INTRODUCTION

Knowledge of the direction of Earth's gravitational field with respect to the body is fundamental to a number of perceptual and motor processes, such as orienting relative to the world, estimating our own self-motion and interception of objects falling under the influence of gravity. However, the direction of gravity is not directly sensed and therefore has to be estimated by the brain. Although the neural substrate and mechanisms underlying the estimation of gravity remain a subject of debate, there is evidence that the cerebellum has an important role to play [1, 2]. Here we examine this hypothesis by investigating whether the gravity-estimation process is affected by disease causing degeneration of the cerebellum.

Determining the direction of gravity is problematic because sensory organs that are graviceptive, such as the vestibular otoliths, provide an ambiguous signal. Otolith afferents may produce identical firing patterns when the head tilts relative to gravity or accelerates linearly [3]. To disambiguate these two physical situations, the brain tracks changes in head tilt relative to gravity by integrating a central estimate of the head's angular motion [4, 5]. The integrated rotation signals are used to estimate the change in orientation of gravity relative to the head, which can be used to separate the tilt and translation components contained in the otolith signal [6, 7]. The brain regions involved in this process have only started to become clear, with some lines of evidence suggesting a role for the cerebellum. Purkinje cells in the caudal cerebellar vermis of rabbits have been shown to modulate their spiking behaviour in response to rotational visual and vestibular cues [8, 9]. In Rhesus macaques, Purkinje cells in the caudal cerebellar vermis encode estimates of both head tilt and translation, which when summed are equivalent to the output of the otoliths [2, 10]. It would seem the caudal cerebellum in monkeys has access to all the signals necessary to implicate it in the estimation of the orientation of gravity and consequently the perception of vertical. However, the perception of vertical is not affected by midline atrophy of the human cerebellum [11]. Although this finding suggests that the orientation of gravity may not be represented in the human cerebellum, it does not preclude a role for the cerebellum in the dynamic process of gravity estimation.

Some evidence for this comes from the findings of Bunn and colleagues [12] when they examined sensory-evoked postural responses in patients with spinocerebellar ataxia type 6 (SCA 6). SCA 6 is a good model of cerebellar dysfunction because its expression is confined largely to Purkinje cells [13] making it an almost pure cerebellar disorder, even after many years of disease duration [14, 15]. SCA 6 patients exhibited grossly exaggerated postural responses exclusively to rotatory visual motion stimuli, with fairly normal responses to vestibular and proprioceptive stimuli [12]. Part of the postural response to vertical-plane visual rotation has been suggested to represent a realignment of the body towards a biased estimate of gravity’s orientation [16]. This follows from the known perceptual bias of gravity’s orientation caused by such visual stimuli [17], which presumably arises from the aforementioned brain’s reliance on angular motion cues to estimate the head’s orientation relative to gravity [18, 19]. Based on this hypothesis, we would predict that SCA 6 patients’ perception of vertical, like their postural response, should be excessively biased by visual rotation. However, this prediction does not provide any insight into the reason for an exaggerated effect of visual rotation in SCA 6. A possible clue comes from the way the brain is believed to combine multi-sensory information to arrive at a unitary perception. An influential model of multisensory integration is maximum likelihood estimation, in which each sensory channel that carries relevant information is weighted by the inverse of the signal's variance, such that the noisier it is, the less it contributes to the final perception [20, 21]. Such an approach has recently been used effectively to model static tilt perception [22, 23]. In dynamic contexts, the brain may combine visual and vestibular rotation cues in this way to arrive at a single estimate of self-rotation [19]. Excessive weighting of visual rotation cues could then arise from disproportionately noisy vestibular cues caused by cerebellar degeneration.

Based on this hypothesis, we predict that cerebellar patients' perception of vertical should be excessively biased by visual rotation due potentially to an increase in vestibular noise relative to visual noise. Here we have tested this prediction by measuring dynamic estimates of vertical during large-field visual-motion stimuli in healthy young controls, healthy age-matched controls and SCA 6 patients. By adding noise to the visual-rotation signal it should be possible to reduce the visual weight when combined with the zero-mean vestibular-rotation signal. The theory predicts that the bias of vertical should increase with higher visual-rotation velocities, but get smaller with the addition of visual noise. Most importantly, based on the principles of multisensory integration using maximum likelihood estimation [20], the effects of visual velocity and visual noise should show predictable differences when combined with the noisier-than-normal vestibular cues hypothesised for SCA 6 patients.

RESULTS

Participants were seated facing a screen on which an annulus of multi-colored dots was projected (**Figure 1A**). At the center of the annulus was a series of white dots arranged in a line whose orientation was controlled by the participant rotating a handheld potentiometer. The line of dots moved as if they were embedded in a solid bar. During trials, the ‘bar’ was continuously perturbed by low-frequency noise while participants were required to try and keep it vertical. At the start of each trial the annulus of dots was stationary for 10 seconds. During this period, all three groups were correctly able to orient the bar to vertical (**Figure 3A**). Young participants' average bar-angle was -0.03 ˚ and their average standard deviation was 0.86 ˚, aged participants average bar-angle was 0.01 ˚ and their average standard deviation was 1.00˚ and SCA 6 participants average bar-angle was 0.07 ˚ and their average standard deviation was 1.16 ˚ (**Figures 2 and 3A**). The absolute value of the bias during the pre-stimulus baseline is illustrated for each group in Figure 3A.

After the first 10 seconds of the trial the annulus of dots began rotation at one of two angular velocities (4 ˚/s or 16 ˚/s) in either the clockwise or counter-clockwise direction. During visual rotation, perceived vertical was biased in the direction of the dots' rotation for all participants. This bias corresponds, in direction, to the bar orientation that would be expected if the participant were rotated in the opposite direction to that of the dots and asked to indicate vertical. The bias increased and plateaued with an approximate time constant, averaged across conditions, of 9.0 ± 3.6 s in young, 7.8 ± 3.0 s in aged participants and 9.8 ± 2.8 s in SCA 6 participants (**Figure 2**). In general, SCA 6 participants were influenced most by visual motion, followed by the aged and then the young participants (**Figures 2 and 4**). Within the

SCA 6 participants, pooled across all conditions, there was a small to moderate significant correlation between the z-scored bias magnitude and disease symptom severity measured by the SARA score ($r = 0.27$, $p = 0.0391$). In addition to varying the velocity, visual noise was manipulated either by having the annulus of dots rotate with coherent motion (zero noise) or by adding noise to the dot's motion. Both visual velocity and visual noise moderated the biasing effect of the stimulus. The relative effect of noise with the average bar angle removed for the two velocities is shown in **Figure 3B**.

To quantify the effect of the visual stimulus across participant groups, conditions and over time, we analyzed the data from the longitudinal nested design (**Figure 1C**) with a multilevel mixed-effects statistical model. We quantified improvements in the fit of the multilevel mixed-effects model caused by the addition of interactions between terms using the likelihood-ratio test. The outcomes of the likelihood-ratio test are presented as a chi-squared statistic in **Table 1**. The inclusion of all 2-way interactions, other than the trial by velocity interaction, improved the fit of the multilevel mixed-effects model. Selected interactions were further decomposed using Bonferonni corrected pairwise comparisons (**Table 2**).

Effects of group

When averaged across conditions and trials, SCA patients were biased to a significantly greater degree by visual motion than aged participants (corrected $p = 0.005$, **Table 2**) and young participants (corrected $p < 0.001$). Aged participants were also biased to a significantly greater degree than young participants ($p = 0.033$).

These differences between groups were dependent on the velocity and noise of the dot motion, as well as the trial number.

Effects of visual velocity and visual noise

Increases in velocity were accompanied by a larger bias in perceived vertical in both SCA 6 (corrected $p < 0.001$) and aged participants (corrected $p < 0.001$) but after correction not in young participants (corrected $p = 0.066$; **Figure 4, Table 2**). However, the influence of velocity differed depending on the group ($\chi^2_{(5)} = 101.13$, $p < 0.001$: **Table 1**). SCA 6 participants were influenced more than aged participants and young participants (corrected $p = 0.002$, $p < 0.001$, **Table 2**), but young and aged groups did not differ (corrected $p = 0.389$). Generally, as velocity increases the mean differences between groups also increases (**Figure 4)**.

The addition of noise to the dots' motion decreased the biasing effect of the visual rotation, but the size of its influence depended on the participant group ($\chi^2_{(2)} = 9.4$, $p = 0.0091$, Table 1), the stimulus velocity ($\chi^2_{(2)} = 83.73$, $p < 0.001$) and the trial number ($\chi^2_{(1)} = 5.81$, $p = 0.016$). Averaging across levels of velocity and trial, visual noise had a significant effect in all groups: young participants (corrected $p = 0.037$), aged (corrected $p < 0.001$), and SCA participants (corrected $p < 0.001$; **Table 2**), but it had a larger effect in SCA 6 ($p = 0.044$) than in young participants (**Figures 4, Table 2**) with aged participants exhibiting an intermediate response. The addition of noise also had a larger effect at higher velocities than at lower velocities (Corrected $p < 0.001$, **Table 2**). Considering that SCA patients are biased to a greater degree than controls, if we divide the change in bias, due to a change in noise or velocity, by the no-noise or 16 deg/s condition within each group, the effect of noise and velocity are very similar between groups (**Figure 3C**). The larger effect of velocity and noise in SCA patients is therefore related to their much greater bias in perceived vertical.

Habituation to visual rotation

Trial order had a significant influence on the biasing effect of the visual stimulus, but was dependent on the group ($\chi^2_{(3)} = 22.13$, $p < 0.001$, Table 1). In both the young and aged participants, the bias in perceived vertical decreased over successive trials of the same condition suggesting an effect of habituation. In contrast, SCA 6 participants did not habituate to the stimulus (**Figure 4**). The trial order trend observed in SCA 6 was different to the trend observed in young participants (Corrected $p < 0.004$) and aged participants (Corrected $p < 0.004$), whereas the trial order trends of the aged and young participants did not differ from each other (Corrected $p = 1.00$; **Table 2**).

Because the overall group differences in the biasing effect described earlier could be influenced by the different degrees of habituation between groups, to test our hypothesis regarding differences between groups, we compared groups using only the first trials of each condition. Prior to any effects of habituation, significant differences between groups remained in these very first trials. Thus, aged participants were biased to a greater degree than young participants (Corrected $p = 0.008$; **Table 2)** and SCA 6 participants were biased significantly more than both aged (Corrected $p = 0.031$) and young participants (Corrected $p < 0.001$).

Sensory cue combination model

To determine if the differences between groups prior to habituation could be explained simply as an increase in vestibular noise, we modelled the first trial data as a process involving visual-vestibular integration using maximum likelihood estimation. We assumed that perceived vertical can be described as the product of two Gaussian likelihood distributions that indicate the likelihood of vertical's orientation given the sensory signals. One is the vestibular likelihood, which is centered at zero since there is no physical motion, with unknown variance that is free to vary between the three groups. The other distribution is the visual likelihood, which is centered at some unknown value and with an unknown variance that is free to vary between the two visual-noise conditions. The mean of each of these distributions can be thought of as the average likelihood of vertical that might be inferred over time from the sensory data, in the absence of the other senses' data, given the environmental context that we may be tilting. The normalized product of the two distributions should then produce a mean bias that is somewhere between the two unimodal means, but with a variance that is smaller than either of the two unimodal variances. For illustrative purposes, the different distributions are shown in **Figure 5A**. We fit the model to all conditions at once but for three individual subjects at a time, with one subject drawn randomly from each group. The model was fit 10000 times to estimate confidence intervals for the fit (Figure S1. Related to Figure 5). On average, the model fit the data best with a vision-only likelihood function that produced a mean bar angle bias of 49 ± 6˚ in response to 16 ˚/s visual motion, and a 26 ± 6˚ bias in response to 4 ˚/s motion. The standard deviation of the vision-only likelihood function was estimated to be 11 ± 3˚ for coherent visual motion and 18 ± 4˚ for the noisy motion. The vestibular-only likelihood function's standard deviation decreased between participant groups from 14 ± 4˚ (SCA) to 10 ± 5˚ (aged), and 6 ± 3˚ (young). The model fit the data with an r^2 of 0.84 ± 0.1 on average and an average root-mean-square deviation in bar angle of 3.4 ± 1.4˚. The model not only captured the main effects of visual noise and visual velocity, but it also captured the effects of group (**Figure 5B**), the group by velocity interaction and the weaker group by noise interaction.

DISCUSSION

Our prediction, that SCA 6 participants' perception of vertical would be excessively biased by visual rotation, was supported by the data. Depending on the condition, visual rotation biased the perceived vertical of the SCA 6 group by up to three times that of the young participants and one and a half times that of the older age-matched group. These results suggest that the human cerebellum participates in the process of estimating the orientation of gravity through its operation on vestibular signals. Its influence appears primarily directed at the processing of dynamic rather than static cues. That is, SCA 6 patients did not exhibit much difficulty orienting the bar to upright during the initial 10 s of trials when the visual scene was static, indicating that when motion cues are absent they are able to accurately indicate vertical, in agreement with previous findings [11]. This suggests that the locus of gravity-orientation perception may be external to the cerebellum, which would be consistent with the finding that transcranial magnetic stimulation over the supramarginal gyrus can alter perceived orientation of vertical [24], but apparently at odds with the finding of head-tilt encoding neurons within the cerebellum [2]. However, this can be resolved if the cerebellum is regarded as contributing to the estimation of change in orientation with respect to gravity.

Moment-to-moment changes in self-orientation with respect to gravity can be estimated from the angular velocity signals encoded by the visual and vestibular systems. Theoretically, summing these changes over time could provide an estimate of self-orientation at any given moment, but small errors would inevitably accumulate eventually leading to large perceptual errors in position. The summing process, therefore, would be useful for estimating short-term dynamic changes but less so for estimating steady-state orientation. Recent theoretical models support this premise through two internal feedback loops in the brain. The first of these, described as somatogravic feedback, acts like a leaky integrator to slowly pull the brain's estimate of gravity back towards the otolith's output, thereby limiting error accumulation during summing of rotation signals [19]. The second of these feedback loops, described as rotation feedback, in effect acts to adjust the brain's estimate of the head's angular motion so as to also bring the estimate of gravity back into alignment with the otolith signal [19]. For both feedback loops, their influence increases as the difference between the internal estimate of gravity and the otolith signal increases [19]. Mechanisms of this sort could explain why the bias in vertical tended to saturate with a long time-constant (~10s) even though the visual scene continued to rotate at a constant velocity. The final tilted position thus represents an equilibrium point between the otolith signal, the two feedback loops and the continued biasing influence of the prolonged visual stimulus on the estimated orientation of gravity. It also explains how disturbed self-rotation signals can coexist with an intact appreciation of upright under static conditions.

More important to our hypothesis, however, is the aspect of the gravity estimation process that is compromised by SCA 6 to produce the observed exaggerated effect of visual rotation. Rather than being a direct result of disordered visual processing, we hypothesised that it could be an indirect effect of disordered vestibular processing. This emerges from the theory of combining sensory cues in a statistically optimal fashion. According to theory, independent vestibular and visual self-rotation signals are weighted such that a signal's weight is inversely proportional to its relative variance, and then combined to give a unitary estimate of self-rotation. This phenomenon was readily apparent in the present experiment when noise was added to the visual-rotation signal. The effect was to increase the signal's variance, hence reduce its weight and its bias of vertical. For the same reason, we postulate that an abnormally large variance in the SCA 6's vestibular self-rotation signal relative to their visual signal could explain their excessive vertical bias to visual rotation. Moreover, changing only the vestibular variance turned out to have strong explanatory power for other measured differences between the three groups. It predicted the interaction between group and visual-rotation velocity as well as the interaction between group and visual noise. By the same token, when patients with bilateral vestibular deficit are exposed to visual motion their perceived vertical is biased to a much greater degree than healthy controls [25, 26]. However, the proposed increased vestibular noise in SCA 6 presumably arises primarily from disturbed cerebellar processing of vestibular signals [1].

Vestibular signals are processed at several locations in the cerebellum such as the vermis, flocculus, nodulus parafloculus and cerebellar lobules as well as in the nearby vestibular nuclei [27, 28, for review see: 29]. During the progression of SCA 6, each of these cerebellar regions experience varying degrees of cell loss [30]. Given such selective degeneration of central regions of vestibular processing it is not surprising that SCA 6 patients exhibit symptoms of central vestibular pathology but are generally absent from symptoms of peripheral vestibular pathology [31, 32]. Such an anatomically focused degeneration suggests that the introduction of vestibular noise into orientation processing would occur during processing in, or transit through, cerebellar or brainstem regions and not at the peripheral end organ. In addition, because of these central vestibular deficits, SCA 6 patients may also exhibit decreased precision in orientation estimates that the vestibular system contributes to, similar to patients with central vestibular disorders [33], due to increased central vestibular noise. Moreover, visual-vestibular symptoms that often present in SCA 6 patients are nystagmus and difficulty visually tracking moving objects [14]. It is possible such visual deficits could influence weighting between vestibular and visual information. Arguably, however, if these oculomotor problems were to have a detrimental effect on visual motion processing, the effect would, if anything, be to increase visual uncertainty and so decrease rather than increase visual weighting.

A potential argument against the idea of increased vestibular noise in SCA 6 comes from the postural responses of SCA 6 patients to stimulation of independent sensory modalities. Bunn et al., [12] showed that SCA 6 patients have abnormally large postural responses to visual-rotation stimuli, in agreement with the current results. Yet postural responses to galvanic vestibular stimulation, a stimulus that simulates a vestibular rotation in the vertical plane when the head is upright [34], were not smaller than healthy control values when viewing a black and white striped screen [12], as would be expected if vestibular weighting were reduced relative to other sensory sources. One explanation could be that overall the sensori-motor output to input relationship (gain) is increased in SCA 6 patients because of their greater baseline instability during stance [35]. Vestibular-evoked postural responses scale with the degree of instability [36, 37] and therefore unstable participants should have larger responses. An overall increase in gain, due to instability, combined with a relative decrease in vestibular weighting, due to increased vestibular noise, could potentially bridge these two observations. However, it is important to note that postural orientation does not necessarily need to mirror subjective visual vertical as measures of postural and visual vertical can sometimes diverge [33, 38].

While we make the argument that participant's behaviour during a dynamic subjective vertical task can be explained simply by an increase in vestibular noise, it remains unclear how cerebellar degeneration might affect other gravity related visual processing. Recent evidence suggests that along with the temporo-parietal junction (TPJ) [39], the cerebellum and vestibular nuclei also contribute to the process of predicting visually represented gravitational acceleration [40, for review see: 41]. If such processing occurs downstream from verticality estimation, relies on common models of gravity or such noisy vestibular cues, we might expect them to exhibit correlated deficits. Ultimately, we cannot rule out the presence of gravity related visual impairments resulting from cerebellar degeneration.

Cerebellar degeneration appears to play a limited role in the active combination of sensory cues contributing to orientation perception, since the maximum likelihood model, under the assumption of a change in the reliability of vestibular cues, fit the behaviour of all participant groups suggesting integration for this particular task may follow cerebellar processing. However, vestibular convergence with visual signals does occur nearby and within the cerebellum [42-45], but is thought to serve gaze-stabilization, reflexive eye movements or posture rather than orientation perception. Indeed, visual and vestibular convergence is suppressed in the fastigial and vestibular nuclei when gaze is fixed [27]. In contrast, cortical regions near the dorsal middle superior temporal cortex (MSTd) and ventral intraparietal cortex (VIP) of monkeys and the analogous TPJ in humans have recently been associated with visual and vestibular cue integration for self-motion and orientation perception. In monkeys, neurons in MSTd and VIP encode visual and vestibular motion signals for self-motion estimation, signals that are also useful for orientation estimation [46-49]. While both areas process visual and vestibular information, MSTd in particular, exhibits integration like behaviour and is a probable site for such multi-sensory cue integration [48]. In humans, the anatomical human homologue to areas MSTd and VIP in monkeys is the TPJ and surrounding region, and it is also thought to be a prominent multisensory integration area. Activity in TPJ correlates with perceived changes in self-location [49] and this region has been proposed to fix the perceived orientation of one's self relative to the world [for review see: 50]. Virtual lesion of the supra marginal gyrus, a region within the TPJ, using continuous theta burst transcranial magnetic stimulation (TMS), causes biases in perceived vertical [24] supporting the region's proposed importance to orientation perception. Together these results suggest that multisensory integration for orientation perception may lie in the TPJ region and this may be why we see no changes in multisensory integration with cerebellar degeneration.

Aging also appeared to play a role in visual rotation’s influence over the perceived vertical. Age-matched controls generally exhibited responses that were larger than those generated by young participants. In addition, age-matched controls exhibited intermediate sized responses when presented with noisy visual stimuli compared to young controls and SCA 6 patients. While this is not the first time enlarged responses have been seen with aging [51] it raises the question of why visual weight should increase with age. With our cue-combination model the behaviour of the aged group, like the SCA 6 group, could be well explained by a change in the variance of the zero-mean vestibular rotation signal. The best fit was given for aged participants when vestibular variance values were intermediate between the SCA 6 and young groups. Given our data, it would seem plausible that cerebellar atrophy may partly contribute to this. Indeed, the cerebellar hemispheres and vermis experience a reduction in volume of approximately two percent per decade and begin to exhibit this trend starting around middle age [52]. In addition to cerebellar decline, the number of human vestibular hair cells continuously declines as we age, dropping in some cases by up to 40% as we reach 70 years of age [53, 54]. Furthermore, vestibular neurons of both central and periphery origin also significantly decreased with age [54, 55] and is seemingly related to an increase in motion discrimination thresholds [56]. Ultimately, age-related cerebellar atrophy and vestibular degeneration could act to increase noise along the vestibular pathways reducing the precision of the vestibular motion estimate. Presumably, similar changes would have occurred in the SCA 6 group, but with the impact of additional noise contributed by the degenerated cerebellum.

Finally, one other difference in behaviour was observed between the SCA 6 and control groups. The amplitude of healthy participants' bias in perceived vertical was reduced over repeated trials, although this conflicts with prior reports indicating no habituation to repeated exposure to rotating visual scenes [57]. The apparent discrepancy may reside in the difference in exposure duration between the two studies. Yardley [57] ceased exposure to the stimulus once vertical was indicated, whereas we continuously exposed participants to the full thirty-second stimulus during each trial. Our increased stimulus presentation time may have heightened the habituation. Interestingly, habituation was not observed in SCA 6 patients, which, if not taken into consideration, contributes to their overall enlarged average responses. This suggests a cerebellar role in the habituation process, consistent with the many reports of cerebellar disease reducing the normal exposure-dependent changes in behaviour to a variety of sensorimotor challenges [58, 59]. The relationship between the impaired habituation we observed and longer-term adaptation or learning is unclear. Recent attempts to use visual motion as a balance-training tool in SCA 6 have met with some success [60] indicating at least partial independence of these mechanisms.

In conclusion, our findings provide the first evidence that the human cerebellum contributes to the estimation of orientation relative to gravity. The data suggest that the cerebellum operates on vestibular signals to provide a vestibular estimate of self-rotation that is then optimally combined with a visual estimate of self-rotation. For this reason, cerebellar degeneration, and aging to a lesser extent, increases uncertainty of the vestibular component relative to the visual component, resulting in an increased weighting of visual rotation signals for estimating dynamic changes in orientation.

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AUTHOR CONTRIBUTIONS

Conception, methodology CJD and BLD.; Software CJD; Formal Analysis, CJD.; Investigation CJD, AP and BLD.; Resources, BLD and PG.; Writing – Original Draft CJD and BLD.; Writing – Review & Editing, CJD, BLD, AP, PG.; Visualization, CJD.; Supervision, BLD.; Project Administration, AP, CJD, BLD.; Funding Acquisition, CJD, PG, BLD.

Declaration of Interests

The authors declare no competing interests

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Figure Legends:

Figure 1. Experimental set up, single subject data and the time-period used to average bar angle. A. Participants sat, head fixed, controlling the angle of the line of white dots (the bar). The annulus of colored dots surrounding the bar could rotate either clockwise or counter clockwise. Participants were tasked with keeping the bar vertical for the duration of the trial. **B.** Single trial subject data from a 16˚/s coherent motion condition in a young participant. The top panel is the angle of the bar, in degrees, for the duration of the trial. The middle panel is the low frequency noise added to the bar, in degrees, to coerce participants to continuously adjust the bar to maintain its position. The bottom panel is the subject's bar-angle time-series, in degrees, averaged across the eight 16 ˚/s coherent motion conditions. The stimulus starts at ten seconds and ends at forty seconds. **C.** Graph of the statistical layout of the experiment. Group and subject were combined during the coding of the statistical test in order to produce a hybrid variable 'id' (Model Level 3) in which condition was nested (Level 2) and trial nested within condition (Level 1). Coherent motion trials: Coher. **D.** Data between the two vertical segmented lines defined the period over which bar-angle bias was measured and compared across conditions. The data presented in panel D is the bar angle, in degrees, averaged across all young participants (n = 15) for the two coherent motion conditions.

Figure 2. Average participant responses over time to full field visual motion for each group and condition.

Plotted are the grand-mean time-series for each condition from each group. The shaded region is the 95 % confidence interval of the mean and the bar below the data in each plot indicates the period over which the visual scene was rotating. Each group is indicated by color and line segmentation: young (red, small dots, n = 15), aged (green, segmented lines, n = 15) and SCA (blue, solid line, n = 15)

Figure 3. Pretrial variance, centered main effects and main effects normalized by the no-noise or 16 deg/s conditions. **A.** Example of the mean rectified bar-angle for the ten seconds prior to the start of motion for all subjects. At the start of each trial, the bar was randomly orientated between 45 ° and - 45 °. None of the groups had difficulty orienting the bar to vertical prior to stimulus motion. Shaded area for each group indicates the standard deviation within each subject averaged across all subjects at each point in time prior to visual motion onset. Zero indicates the bar is vertically oriented. Group is indicated by color and line segmentation: young (red, small dots, n = 15), aged (green, segmented lines, n = 15) and SCA (blue, solid line, n = 15). **B.** The effect of noisy stimulus motion. The data, averaged across all subjects within each group for each condition, was centered in order to compare trends between each group, by subtracting the average bar-angle between the two motion conditions in each group. At 4 °/s, the aged group and young group behave similarly with the addition of noise. SCA patients have a much larger decrease in bar-angle than either control group with the addition of noise. At 16 °/s, both SCA patients and the aged control group behave similarly with the addition of noise, whereas young controls appear to be influenced less. Error bars indicate the 95 % confidence interval of the mean. Noisy motion trials: Noisy, Coherent motion trials: Coher. In the figure, group is indicated by color and line segmentation: young (red, small dots, n = 15), aged (green, segmented lines, n = 15) and SCA (blue, solid line, n = 15). **C.** Main effect of noise and velocity normalized by the coherent or 16 deg/s condition. When normalized, the difference in bar angle induced by adding

noise (left) or by decreasing velocity (right) to the bar angle in the coherent (left) and 16 deg/s conditions (right) is reduced between groups. Values are the ratio of the difference between conditions divided by the coherent or faster condition ([4deg/s coherent - 4deg/s noisy] / 4deg/s coherent; [16deg/s coherent - 16deg/s noisy] / 16deg/s coherent and [16deg/s noisy - 4deg/s noisy] / 16deg/s noisy; [16deg/s coherent - 4deg/s coherent] / 16deg/s coherent). Error bars are the 95% confidence intervals for the means. Group mean (large filled circles) and each participant's mean (small filled circles) are displayed in both panels using separate colors for each group: young (red, n = 15), aged (green, n = 15) and SCA (blue, n = 15).

Figure 4. Mean bar-angle for each condition generated by bootstrapping the mixed-effects model, including bootstrapped 68 % and 95 % confidence intervals with the mean subject data superimposed. To give a sense of the data's variability the errors bars on the mean subject data are two standard deviations. In general, the model indicates that bar-angle was biased to a greater degree at faster velocities than slow, and the addition of noise decreased the biasing effects of visual motion. However, the influence of stimulus velocity depended on the participant’s group, with SCA patients most influenced by an increase in stimulus velocity. The influence of noise was also dependent on the participant group, as the largest reduction in bias due to noise occurred in the SCA patients significantly more than young controls whereas older adults exhibited an intermediate response. Lastly, there was an interaction between group and trial with both young and aged participants exhibiting habituation over time whereas SCA patients did not. In the figure, group is indicated by color and line segmentation: young (red, small dots, n = 15), aged (green, segmented lines, n = 15) and SCA (blue, solid line, n = 15). Velocities are organized by column and the presence of noise by row. Confidence

intervals for the multi-level model were derived by sampling with replacement from the raw data. We then fit the model to the sampled data to get a predicted bar angle for each sample. This process was repeated 10,000 times. Then the average prediction and confidence intervals across the bootstrapped samples were obtained for each time point, velocity, noise, and group.

Figure 5. Cue Combination model compared to the average bar angle for the first trial of each condition. A. shows the variables used and outlines the layout of the model. The whole model was fit at once, with the vestibular mean fixed at zero, the vestibular standard deviation held constant across rows and the visual mean and standard deviation held constant within columns. Within each column, only the vestibular standard deviation was free to vary. Probability density functions illustrate the cue-combination within each condition and group. ML (Black) is the maximum likelihood estimate which is the combination of the visual (vis) and vestibular (ves) derived bar angle distributions.

B. The model captures both the effect of velocity and noise but overestimates the effect of noise in aged and young participants in the 4 ˚/s. The colored squares are empirical data from the first trial of each condition whereas the model fit is shown by circles. Error bars are the 95% confidence intervals for the means. Each group is displayed using separate colors: young (red, n = 15), aged (green, n = 15) and SCA (blue, n = 15).

Table 1

Likelihood Ratio Test

Interaction Added	Chisq	Df	P-value	Signif
Velocity by Group	101.13	5	2.2×10^{-16}	***
Noise by Velocity	83.73	2	2.2×10^{-16}	***
Noise by Group	9.39	2	0.0091	**
Trial by Group	22.13	3	6.1×10^{-5}	***
Trial by Noise	5.81	1	0.0159	*
Trial by Velocity	0.64	1	0.4225	

Table 1. Influence of interactions added to the multilevel mixed-effects model compared via the likelihood ratio test (n = 45). The inclusion of three-way interactions did not improve the fit of the multilevel mixed-effects model over a two-way interaction only multilevel mixed-effects model. Chi-Square Statistic (Chisq), Degrees of Freedom (Df), Significance (Signif). * $p < 0.05$ and $p > 0.01$, ** $p < 0.01$ and $p > 0.001$, *** $p < 0.001$

Table 2.

Group	Contrast	Estimate	Std. Err.	Df	t - ratio	P-value	Signif
*Young vs Aged	(Trial 1)	-6.28	1.97	45	-3.174	0.0027	**
*Young vs SCA		-11.57			-5.853	< 0.0001	***
*Aged vs SCA		-5.3			-2.679	0.0103	*
Young vs Aged		-6.28	1.89	45	-3.330	0.0017	*
Young vs SCA		-13.73			-7.284	< 0.0001	***
Aged vs SCA		-7.46			-3.954	0.0003	**
Young	16˚/s vs 4˚/s	-2.77	0.93	135	-2.974	0.0035	
Aged		-5.85			-6.292	< 0.0001	***
Sca		-11.03			-11.874	< 0.0001	***
Young vs Aged	16˚/s vs 4˚/s	3.08	1.31	135	2.346	0.0205	
Young vs SCA		8.27			6.292	< 0.0001	***
Aged vs SCA		5.19			3.947	0.0001	**
Young	Coh. vs Noisy	2.94	0.93	135	3.160	0.0020	*
Aged		5.27			5.672	< 0.0001	***
SCA		7.02			7.554	< 0.0001	***
Young vs Aged	Coh. vs Noisy	-2.34	1.31	135	-1.776	0.0781	
Young vs SCA		-4.08			-3.106	0.0023	*
Aged vs SCA		-1.75			-1.330	0.1856	
16˚/s vs 4˚/s	Coh. vs Noisy	-6.73	1.07	135	-6.73	< 0.0001	***
Young vs Aged	Trial	-0.01	0.15	45	-0.005	0.9960	
Young vs SCA		-0.62			-4.075	0.0002	**
Aged vs SCA		-0.62			-4.072	0.0002	**

Table 2. Selective decomposition of the multilevel mixed-effects model using marginal means. P-values are uncorrected. Stars in the right column represent statistical significance after correction. The first three comparisons (starred in the left column) are corrected only for their within group comparisons (critical p-value divided by 3), due to their hypothesis driven nature, whereas the remaining comparisons were corrected by dividing the critical p-value by 19. Standard Error (Std. Err.), Rounded Satterthwaite derived Degrees of Freedom (Df), p-value (P-value), Bonferonni corrected significance (Signif). * $p < 0.05$ and $p > 0.01$, ** $p < 0.01$ and $p > 0.001$, *** $p < 0.001$

STAR Methods

CONTACT FOR REAGENT AND RESOURCE SHARING

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Prof. Brian Day (brian.day@ucl.ac.uk).

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Fifteen participants with spinocerebellar ataxia type 6 (SCA 6) (8 males and 7 females, mean age of 67 ± 10 yrs) were recruited from the Ataxia Centre at the National Hospital of Neurology and Neurosurgery. They had a mean score of 12 ± 8 on the Scale for Assessment and Rating of Ataxia (SARA) [61]. Participants with SCA 6 were included if they were over the age of 18 and their diagnosis had been genetically confirmed. Fifteen participants (7 males and 8 female, mean age of 63 ± 9 yrs), approximately matched in age to the participants with SCA, were recruited for this study from the local population via an advertisement. In addition, fifteen healthy young adult participants (6 males and 9 females, mean age 25 ± 5 yrs) were recruited from the local university population using an advertisement. Prior to participation, the experimental protocol was explained to each participant and the participant’s informed written consent obtained. All procedures in this study conformed to the declaration of Helsinki and were approved by the National Research Ethics Service Committee.

METHOD DETAILS

Participants were excluded from participation based on the following criteria: being outside the ages of 18 and 80 years old, neurologic or orthopaedic condition (outside of SCA 6), pregnancy, current registration as blind, absent proficiency in the English language and absent competency to provide consent. A statistical power calculation was not feasible due to a lack of available relevant data for the SCA group. Instead, the sample size was balanced between groups and determined on a pragmatic basis based on prior experience with this clinical cohort and the availability of suitable patients with this relatively rare condition.

Participants sat with their head fixed by a chair-mounted clamp, 60 cm in front of a 2.4 m wide rear projection screen (The Widescreen Center Ltd, London, UK). An annulus of multi-coloured dots (244 cm outer diameter [visual angle 128 ˚], 48 cm inner diameter [visual angle 44 ˚], density 1460 dots/m^2) was projected (Infocus DLP SP860, Portland, OR, USA) onto the screen in front of them (**Figure 1A**). The annulus encircled a yoked linear sequence of 17 white dots, each with a diameter of 15 mm (visual angle 1.4 ˚) and separated from each other by 14 mm (created in LabVIEW: National Instruments, Austin, TX, USA), which participants aligned with the perceived orientation of vertical. Dots were used instead of a solid bar in order to limit the verticality cues that can arise from pixelation along the edges of a solid bar, when it is not vertically oriented. Because the dots were in a line, moved with rigid motion and rotated about the group's centre, we will refer to them as a 'bar'. Participants controlled the angle of the bar using a handheld potentiometer and were tasked with keeping the bar vertical for the duration of each trial. In order to compel participants to provide a continuous estimate of vertical a small amount of low-frequency noise was added to the angular position of the bar (0 - 0.2 Hz bandwidth, mean of 0 ˚, standard deviation of +/- 9.6 ˚, range of +/- 35.9 ˚ [**Figure 1B**]). Trials began with the bar oriented randomly between 45 ˚ and - 45 ˚. For the first 10s of each trial, participants could control the angle of the bar but the annulus of dots surrounding the bar remained stationary. After the initial ten-second static period, the annulus of dots rotated for thirty seconds in either the clockwise or counter-clockwise direction, at one of two angular velocities (4 ˚/s or 16 ˚/s), with either coherent or noisy motion. The specifics of the noise are described in detail below. The rotation finished with the annulus of dots returning to a static configuration for an additional ten seconds. Six trials (of 1440) were stopped early in this final 10s period (mean length of 46.28 ± 1.98s), and therefore we present this data for illustrative purposes only (Figure 2). Each trial lasted fifty seconds and participants were required to maintain the vertical position of the bar for the duration of the trial. All visual-motion stimuli were created in Matlab (Mathworks Inc., Natick, MA, USA) using the Psychophysics toolbox [62, 63]. Data were collected using a custom written LabVIEW program, which recorded the angular position of the bar, the added noise, the trial code and the time key. All data were sampled at 30 Hz and the Matlab and Labview programs were synchronized using a custom written software program.

Visual Stimulus: To create the annulus, variable-coloured dots were randomly placed over the screen. Dots less than the inner radius of the annulus and greater than the outer radius of the annulus were removed. During each trial, the dots in the annulus could move with either clockwise or counter-clockwise motion, at one of two speeds (4 ˚/s or 16 ˚/s) and with coherent or noisy motion. During coherent trials, the angular distance each dot moved between frames was constant. Each dot essentially travelled around the center of the annulus on a circle of constant radius. Thus, dots near the outer border travelled a greater linear distance between each frame than dots near the inner border of the annulus. To create the noisy motion, we used a similar approach to Williams and Sekuler [64]. Each dot took an independent noisy walk around the annulus. However, the average angular velocity of all the dots (the field velocity) remained constant at 4 ˚/s or 16 ˚/s. To achieve a constant field velocity, the angle at which each dot was displaced was drawn from a uniform distribution. The range of this distribution was sixty percent of a full circle (± 108 ˚) meaning the angle at which each dot jumped between frames was between - 108 ˚ and 108 ˚. Since the distribution was centered on the intended direction of motion, the average motion of each dot was biased in the intended direction of motion. The dot jump distance was then scaled so that the average motion of the dots was equivalent to one of the two (4 ˚/s or 16 ˚/s) desired field velocities.

Quantification and Statistical Analysis.

Our primary dependent measure was the angle of the bar relative to vertical. We calculated the angle of the bar prior to visual motion to determine if participants could identify vertical without movement in their visual field. For this measure we averaged the bar position for the final two seconds before visual motion began in Matlab (**Data S1**). The standard deviations presented in first paragraph of the results section quantify the mean variability of the pre-stimulus baseline across subjects within each group. The absolute error over this period is shown in Figure 3A. To quantify the exponential shape of subject's responses during visual motion we fit the average time series for the group with an exponential of the form:

$$Y = a(1-e^{(-bx)}) + c$$

Where a, b and c are constants to be fit, x is the time variable and e is the exponent.

To fit the exponential function in matlab (**Data S1**), data were cut to include only the period of visual motion. To better approximate the asymptotic value of the exponential we projected the function 1000s from trial onset. The time constant was defined as the time taken for the exponential to reach 63% of its estimated maximum value.

To quantify the influence of visual motion, trials with similar velocities and noise levels were pooled across motion directions after being re-based by their average value between five and ten seconds. Prior to pooling, mean responses between twenty-seven and forty seconds within each subject from conditions with similar direction, velocities and noise were averaged and the clockwise trials inverted. Conditions were then compared in Matlab (**Data S1**), using a paired t-test ($P < 0.05$), across motion direction to determine whether the two motion directions were significantly different. Since the two directions were not statistically different from each other in any of the groups, the clockwise trials were inverted [25] and pooled with the counter-clockwise trials to provide a single time series for each noise level and velocity for each subject.

To provide a simple measure of the influence of the stimulus across participant groups, we averaged the bar-angle during the period between twenty-seven and forty seconds (**Figure 1d**) for each subject. We identified this interval visually from the response plateau of the grand mean bar-angle time-series for two coherent motion conditions across all the healthy young participants (**Figure 1d**), as their data were the least variable. Due to its hierarchical structure, we modelled the data from the longitudinal nested design in R [65, 66] (**Figure 1c**), using a multilevel mixed-effects model (**Data S1**). Trials common over time were nested within a condition, which were randomized to a cross between noise level and velocity. Each of the four combinations of conditions were themselves replicated and nested within subjects. We compared nested candidate models, differing by the inclusion of fixed effects (Noise, Velocity, Group and their interactions), using the likelihood ratio test

(Table 1). Random effects for time allowed for subject-by-subject variation in the slope and intercept within each model. Interactions were decomposed using Bonferroni corrected pairwise comparisons of the marginal means in R, and are displayed in Table 2. Significance was set at $P < 0.05$.

Single trial data from one of the young participants was removed from comparison due to it being an extreme outlier (outlier: 69 ˚, the subject's remaining trials were 20.2 ˚ ± 5 ˚ [mean ± standard deviation]). The outlier was identified using Tukey's boxplot method in SPSS (IBM) with a threshold of greater than three times the interquartile range.

Data Modelling: We used maximum-likelihood estimation in Matlab (**Data S1**) to predict the effect of group and condition on the average bar angle, which is thought to reflect the brain's estimate of the head's angular velocity [17]. This approach estimates the optimal combination of cues such that their product is the minimum variance solution. Here we assume that the data are normally distributed and thus sensory cues are weighted by the normalized inverse of their variance and summed together [20]. Fits of the average bar angle are given by

$$\overline{CE} = \sum_i w_i \bar{E} \qquad \text{with} \qquad w_i = \frac{\frac{1}{\sigma_i^2}}{\sum_{\mathrm{j}} \frac{1}{\sigma_{\mathrm{j}}^2}}$$

where $\overline{CE}$ is the combined estimate, $\bar{E}$ is the sense's estimated mean, w_i is the weight for the i^{th} sense, σ is the cue's standard deviation with j used to index the summation of the inverse variances across the contributing senses. The sensory cues can be thought of as likelihood distributions centred on the average deviation in bar angle that would occur in absence of the other modality. The vestibular mean was therefore set to 0 ° and the other parameters set according to the sum of least squares fit to the average bar angle data. We expect that the mean unimodal visual likelihoods will exceed the multisensory estimate predicted by the data and the model, similar to the exaggerated responses observed in patients with bilateral vestibular deficits [25, 26, 67]. The only parameter free to vary between groups was the standard deviation of the vestibular estimate. Confidence intervals for the model were estimated via bootstrap using 10,000 draws [68]. Briefly, single subject first trail data for one subject in each group and for each condition was drawn 10,000 times at random with replacement, then the model fit to each draw using gradient descent. To fit each draw, the model was started at 5000 different, but nearby, starting points. The parameters from the starting point which ended with the lowest squared difference cost were taken as the fit and used to estimate the distribution of parameter values around the mean. The 10,000 single subject parameter estimates were averaged in groups of ten and these averages were subtracted from the sample mean to get a distribution of the differences from the sample mean. The difference values were then sorted and the 2.5 and 97.5 percentiles were extracted. For further details see supplemental Figure S1.

DATA AND SOFTWARE AVAILABILITY

Quantification and statistical analysis were performed in Matlab and R and the code has been provided in the file "Data S1". The raw single subject data, zero padded (to make all the files the same length, and converted to .mat files is stored at http://dx.doi.org/10.17632/gypdwfht4s.1 along with the data file used for the multilevel model "All Data.xls" and the maximum likelihood confidence interval data used in the manuscript "Published_CI_Data.mat".

Data S1. Code related to STAR methods. Matlab and R analysis code to reproduce the results in both the text and figures of this manuscript. These scripts are to be run with the raw and processed data stored at http://dx.doi.org/10.17632/gypdwfht4s.1. The Matlab code will reproduce all the results except those for the multilevel model, its decomposition and **Figure 4**, which were coded in R.