Sensorimotor Processing for Balance in Spinocerebellar Ataxia Type 6

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ABSTRACT: We investigated whether balance impairments caused by cerebellar disease are associated with specific sensorimotor processing deficits that generalize across all sensory modalities. Experiments focused on the putative cerebellar functions of scaling and coordinate transformation of balance responses evoked by stimulation of single sensory channels. Vestibular, visual, and proprioceptive sensory channels were stimulated in isolation using galvanic vestibular stimulation, moving visual scenery, and muscle vibration, respectively, in 16 subjects with spinocerebellar ataxia type 6 (SCA6) and 16 matched healthy controls. Two polarities of each stimulus type evoked postural responses of similar form in the forward and backward directions. Disease severity was assessed using the Scale for Assessment and Rating of Ataxia. Impaired balance of SCA6 subjects during unperturbed stance was reflected in faster than normal body sway (P < 0.009), which correlated with disease severity (r = 0.705, P < 0.001). Sensory perturbations revealed a sensorimotor processing abnormality that was specific to response scaling for the visual channel. This manifested as visually evoked postural responses that were approximately three times larger than normal (backward, P < 0.001; forward, P = 0.005) and correlated with disease severity (r = 0.543, P = 0.03). Response direction and habituation properties were no different from controls for all three sensory modalities. Cerebellar degeneration disturbs the scaling of postural responses evoked by visual motion, possibly through disinhibition of extracerebellar visuomotor centers. The excessively high gain of the visuomotor channel without compensatory decreases in gains of other sensorimotor channels provides a potential mechanism for instability of the balance control system in cerebellar disease. © 2015 The Authors. Movement Disorders published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

Key Words: Motor control; balance; cerebellum; spinocerebellar ataxia; clinical neurophysiology

Balance disorders are commonly observed after cerebellar lesions arising from genetic causes, ischemia, tumors, alcoholism, and trauma.1-4 However, we have no clear understanding of the cerebellum’s role in...
balance control or the range of fundamental deficits that might be caused by different cerebellar lesions. Balance control involves acting on information about the body’s current state of stability signaled by multiple sensory modalities. The cerebellum has the potential to participate in this process, because it either directly or indirectly receives considerable multisensory information known to be important for balance, including that from vestibular, proprioceptive, somatosensory, and visual sources. Here we pursue this idea by asking whether cerebellar disease is accompanied by a specific deficiency of sensorimotor processing for balance, and if so, whether the deficiency generalizes across all sensory modalities. To examine these questions, we studied a cohort of patients with spinocerebellar ataxia type 6 (SCA6). SCA6 causes death of Purkinje cells in the superior and anterior parts of the cerebellum and gliosis in the flocculo-nodular lobe, but with little or no extracerebellar involvement. Thus, it is a rare but well-defined and relatively pure form of cerebellar degeneration, which during quiet stance causes clear balance impairments that scale with disease severity.

The classical approach for studying balance is to perturb the body and measure the ensuing response. However, natural perturbations of the body inevitably stimulate multiple sensory systems simultaneously, making it difficult to analyze the processing of information from each sensory channel. The approach we have adopted, therefore, is to stimulate each of the three main sensory channels (visual, vestibular, and proprioceptive) in isolation, using stimuli that do not directly perturb the body but that nonetheless produce well-defined postural responses. The three modes of stimulation were chosen to produce similar postural responses in the same directions so that any differences in response behavior could be attributed to the sensory channel rather than to the motor system generating the response. We consider two fundamental sensorimotor functions that have been proposed for the cerebellum, namely, control of response scaling and coordinate transformation. If response scaling of a sensorimotor loop is deficient, the amplitude of the balance response will be either too small or too large. With a deficiency in the coordinate transformation of information from a sensory to an action coordinate frame, such as from head coordinates to leg coordinates, the direction of the balance response may be incorrect or excessively variable.

Methods

Procedures were approved by the University College London Hospitals NHS Trust ethics committee, and consent was obtained from participants in accordance with the declaration of Helsinki (2004).

Subjects

Sixteen subjects with SCA6 from different families were recruited from the Ataxia Centre at the National Hospital of Neurology and Neurosurgery. Sixteen healthy control subjects (HC) were recruited from a local advertisement and acted as controls matched to patients by age, height, and weight.

Subjects with SCA6 were included if they 1) were 18 y of age or older, 2) had a confirmed genetic diagnosis of SCA6; 3) had a score greater than zero on the Scale for Assessment and Rating of Ataxia (SARA) or nystagmus. Note that subject 3 scored zero on the SARA but had nystagmus and a subjective feeling of unsteadiness. Subjects in either group were excluded if they 1) were unable to walk 10 m unaided; 2) were unable to stand independently for 10 s with their eyes closed; 3) were taking drugs (medication or alcohol) with side effects of dizziness, drowsiness, or muscle weakness; or 4) had current or past medical conditions, other than SCA6, that could affect balance. No subjects reported headaches or migraines within the week before testing.

Clinical Rating of Disease Severity and Sensory Function

The SCA6 subjects were assessed using SARA to provide a measure of disease severity (score: 0 = no ataxia, 40 = most severe ataxia). The Inventory of Non-Ataxia Symptoms was used to screen for non-ataxia signs. Sensory examination was carried out in all SCA6 subjects. Magnetic resonance imaging reports were reviewed to ensure that only those with restricted cerebellar atrophy were included. Ocular examinations were undertaken and the presence of clinically detectable abnormal features recorded, such as nystagmus, oscillopsia, broken smooth pursuit, and ophthalmoplegia. Biothesiometer ascending and descending threshold measures of vibration sensitivity were collected over the central tibialis anterior (TA) and medial gastrocnemius (mGAS) muscle bellies, and monofilament tests of sensitivity to light pressure (10 g) were collected using the standardized procedures outlined previously. Measures of near visual acuity and nature of spectacle use was documented (near/distance correction, uni/bifocal). Subjects were asked whether they had ever experienced or were currently experiencing any vertigo symptoms (dizziness, spinning, nausea, migraines).

Instrumentation

Subjects stood on a force plate (model 9286AA, Kistler, Winterthur, Switzerland) that recorded ground reaction forces. Whole-body motion was recorded using a three-dimensional motion-capture system (CODA, Charnwood Dynamics, Rothley, UK). Rigid clusters of four infrared emitting diodes were fixed using non-slip
elastic straps to the head, the torso (level of C7 verte-
brae), and the back of the pelvis, and three diodes were
attached to each shank and each foot. All signals were
synchronized and sampled at 200 Hz.

Procedure
Unperturbed body sway was initially recorded for
40 s while subjects stood with a 4-cm stance width
(distance between medial borders of the feet), facing a
wall at a distance of 2 m with eyes open. This provided
a measure of baseline instability under conditions that
were shown previously to give the best correlation
with clinical disease severity. For perturbation trials,
the stance width was increased to 8 cm, because
patients were more stable and therefore found it less
tiring when standing for prolonged periods. However,
as shown previously, this increase had no effect on
baseline body sway in the anteroposterior direction.

The three main sensory modalities were investigated
using sensory perturbation techniques: 1) visual per-
turbations in the form of visual motion stimuli (MVS;
cw, clockwise; ccw, counter-clockwise), which leads to
a postural response in the same direction as the scene
movement; 2) vestibular perturbations using galvanic
vestibular stimulation (GVS; r+, anode right cathode
left; 1+, anode left cathode right)), which evokes a
postural response in the direction of the anodal ear; 3)
proprioceptive perturbations using muscle vibration
(VIB; ts, triceps surae; ta, tibialis anterior) of lower leg
muscles, which leads to a postural response in a direc-
tion that shortens the vibrated muscle. To compare
across sensory modalities, the postural responses were
designed to be similar in form, magnitude, and direc-
tion for a healthy standing subject. The response direc-
tions that could be studied were constrained by the
vibratory stimuli, which were applied to ankle flexors
and extensors to produce postural responses in the
anteroposterior direction. For vestibular and visual
stimuli to evoke responses also in the anteroposterior
direction, the head was rotated in yaw through 90
degrees (GVS response is directed approximately along
the interaural line), and the visual scene movement
was limited to rotation in the sagittal plane about the
ankle axis. Technical details of the various stimuli
employed are given in Supplemental Data.

For the perturbation trials, subjects stood with their
feet 8 cm apart and head rotated to the right through
90 degrees to face the visual scene 0.4 m away in the
sagittal plane. This scene remained stationary in all
conditions expect for the moving visual stimulus con-
dition. Subjects wore spectacles or contact lenses if
required and a visual field restrictor that limited vision
to a 74-degree horizontal viewing angle and 32-degree
vertical viewing angle (approximating a 60 × 25-cm
visible screen area). Earplugs (32 dB) and background
white noise masked equipment-related noise. The sub-
ject wore a safety harness that prevented vertical
drops of 5 cm or more.

After a random baseline period of 3 to 4 s, a 2-s
sensory stimulus was given followed by a 5-s post-
stimulation period. Twenty trials of each stimulus (10
per direction) were randomly intermixed with 20 no-
stimulation trials. Trials were randomized according
to stimulus type and its direction. Audible tones sig-
naled the start and the end of each trial. Sufficient
time was provided between stimuli to allow subjects
to adopt the standardized starting position. Rests were
included as required during the tests.

Measurement
Body motion was measured from body displacement
approximately at the level of the C7 vertebra. This
was converted to an angular measure, using the height
of the marker-cluster above ground level. Stimulus-
evoked response mean magnitude and direction were
measured from each subject’s mean traces between
0.2 s and 1.0 s (responses to the moving visual scene
[MVS] were also measured at 2 s). Direction variabi-
ity and habituation were measured from single-trial
responses. Baseline sway speed was calculated from
the 40-s period of quiet stance as total horizontal-
plane path/duration as described previously. See Sup-
plemental Data for measurement details.

Statistical Analysis
Between-group comparisons of response magnitudes
were carried out using two-tailed Student’s t tests for
independent samples (PASW Statistics 18, IBM,
Armonk, NY, USA). Equal variances were not assumed
if Levene’s test of equality of variances yielded P values
less than 0.05. Differences between groups were tested
separately for each sensory stimulation mode (GVS,
MVS, VIB) and direction (forward, backward), yield-
ing six comparisons for each measure. To account for
multiple comparisons, the significance level was set at
P < 0.01. Associations between response magnitude
and disease severity (SARA score) were determined by
using Pearson’s correlation coefficient.

Analyses of response direction were performed using
circular-data statistical procedures described in Sup-
plemental Data.

Results
Anthropometric data, clinical assessments, and base-
line sway speed are detailed in Table 1. All SCA6 sub-
jects scored zero on the Inventory of Non-Ataxia
Symptoms scale, indicating no clinically detectable
non-ataxia symptoms, and all displayed horizontal
gaze-evoked nystagmus with saccadic pursuit.

No group differences in vibration thresholds (TA:
P = 0.689, mGAS: P = 0.225), monofilament testing
(P = 0.657), or near visual acuity (P = 0.704). Mean sway speeds during quiet stance were significantly higher in the SCA6 group (P = 0.009). Sway speed correlated with disease severity assessed by SARA (r = 0.705, P < 0.001).

Figure 1A shows the time-course of the sagittal-plane component of the group mean responses evoked by the three sensory stimuli. The time-course, magnitude, and direction of responses were deemed sufficiently similar to compare the three sensory modalities.

### Response Magnitude

The group mean response magnitudes are shown for each stimulus modality and polarity in Figure 1B. In general, the SCA6 group tended to show larger responses than controls. The magnitude difference was highly significant for MVS (cw: t[17.55] = 5.67, P < 0.001; ccw: t[16.75] = 3.25, P = 0.005) but only showed trends for one of the two polarities for VIB (ts: t[22.91] = 2.09, P = 0.048; ta: t[16.78] = 1.81, P = 0.088) and for GVS (r+: t[29] = 2.51, P = 0.018; l+: t[29] = 0.62, P = 0.540). The MVS response was measured over a different period compared with the VIB and GVS responses (see Methods). However, when measured over the same time period (0.2-1 s), the MVS response magnitude combined for the two directions remained highly significantly larger for SCA6 than HC (SCA6, 0.47 ± 0.06; HC, 0.21 ± 0.02; t[20.10] = 4.23, P < 0.001).

The magnitude of each single-trial response was measured to investigate habituation to repeated presentation of the same stimulus. Plots of response magnitude versus stimulus presentation order (shown in Supplemental Data) indicated a uniform lack of habituation. Thus, the response magnitudes to the first and the ninth presentations were not significantly different from each other for all types of stimulus in both groups of subjects (P > 0.05 in all cases).

### Response Direction

Statistical analyses of the group mean response directions are shown in Table 2. The response directions were significantly concentrated around a mean direction for all stimulus conditions in both groups. No significant differences were seen in mean response direction for the two groups. The dispersion of response directions around the mean, measured by angular deviation reflecting response direction variability within a group, was not significantly different between groups for any stimulus condition, although a trend was seen for a greater dispersion in SCA6 for the VIB-ts condition (P = 0.023).

### Within-Subject Response Direction Variability

Although the directions of the each subject’s mean responses were not different for the two groups, possibly the SCA6 subjects were abnormally variable from trial to trial in their response directions. This was
quantified by calculating each subject’s angular deviation of single-trial responses. Table 3 gives the group mean and variability of this measure and shows that the within-subject response direction variability was not significantly different between groups.

**Correlation of Response Magnitude With Disease Severity**

Response magnitudes were averaged for the two polarities of each stimulus modality and correlated with SARA scores. As shown in Figure 1C, a significant positive correlation was found between SARA and MVS response magnitude \((r = 0.543, P = 0.030)\), but not for GVS \((r = 0.108, P = 0.702)\) or VIB \((r = 0.387, P = 0.138)\).

**Discussion**

We have asked whether the balance instability of SCA6 subjects is associated with a deficiency of sensorimotor processing and, if so, whether the deficiency generalizes across all sensory modalities. As reported previously,\(^4\) balance control of this SCA6 group was abnormal. Even without sensory perturbations, these patients were more unstable than the control group, showing greater body sway during quiet stance, which scaled with disease severity. Despite this instability, many aspects of the responses to single-channel sensory perturbations were largely unaffected. The notable exception was the response magnitude to the visual perturbation, which was considerably larger than control by a factor of 3 on average. If this excessively large response were attributable simply to the underlying enhanced body sway, then all sensory stimuli should have produced similarly large responses. However, the exaggerated response was reasonably specific to the visual modality and was disease-related because it correlated with disease severity measured by SARA. This large mean response could not be explained by differences in the rate of habituation of single-trial responses to...
repeated presentation of stimuli, because neither group showed significant habituation.

Our results do not replicate those of an earlier study on the visual control of balance in cerebellar patients, which employed a “moving room” stimulus not dissimilar from our moving visual scene. However, many differences exist between the two studies, including predictability of the stimulus, response direction, measurement period, and, most importantly, the clinical cohorts investigated (SCA6 vs. heterogeneous etiology).

### Specificity and Mechanism of Sensorimotor Disruption

The two processes under consideration were response scaling and coordinate transformation. The positive finding of enlarged balance responses supports the concept of disrupted response scaling. An abnormality of response scaling is not unlike the exaggerated whole-body response to support-surface perturbation observed in cerebellar patients and may represent another expression of typical cerebellar dysmetria reported for limb movements and eye movements.

A possible explanation for over-scaling is that it arises from cerebellar disinhibition of sensorimotor centers outside the cerebellum caused by a loss of Purkinje cells, which exert tonic inhibitory influence on deep cerebellar nuclei. Why the brunt of the abnormality should fall on the visual channel is not clear. It may have something to do with the fact that visual flow is inherently ambiguous in that it signals motion of the environment as well as self and therefore

### TABLE 2. Response directions measured from mean traces of upper trunk displacements

<table>
<thead>
<tr>
<th></th>
<th>GVS</th>
<th>MVS</th>
<th>VIB</th>
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<tbody>
<tr>
<td></td>
<td>R+</td>
<td>L+</td>
<td>CW</td>
</tr>
<tr>
<td>SCA6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>15</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Mean (°)</td>
<td>-82.95</td>
<td>80.72</td>
<td>-96.30</td>
</tr>
<tr>
<td>Concentration r</td>
<td>0.933</td>
<td>0.944</td>
<td>0.911</td>
</tr>
<tr>
<td>Angular deviation</td>
<td>21.05</td>
<td>19.11</td>
<td>24.15</td>
</tr>
<tr>
<td>HC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Mean (°)</td>
<td>-88.08</td>
<td>72.49</td>
<td>-79.87</td>
</tr>
<tr>
<td>Concentration r</td>
<td>0.937</td>
<td>0.968</td>
<td>0.859</td>
</tr>
<tr>
<td>Angular deviation</td>
<td>20.39</td>
<td>14.44</td>
<td>30.45</td>
</tr>
<tr>
<td>SCA6 vs HC</td>
<td>Mean direction</td>
<td>F</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.515</td>
<td>0.203</td>
</tr>
<tr>
<td>Angular deviation</td>
<td>U</td>
<td>141</td>
<td>142</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>0.423</td>
<td>0.401</td>
</tr>
</tbody>
</table>

Notes: One SCA6 subject did not contribute GVS responses because of technical failure. Response direction is reported relative to the visual screen, with 0° indicating motion directly toward the screen, 90° to the left parallel to the plane of the screen, and −90° to the right. All mean directions were highly significantly concentrated (P << 0.001). Mean directions compared using Watson-Williams test. Angular dispersion compared using Wallraff procedure and tested with two-tailed Mann-Whitney test. P denotes probability, with significance set at P < 0.01.

GVS, galvanic vestibular stimulation; MVS, moving visual scene; VIB, muscle vibration; R+, anode right; L+, anode left; CW, clockwise; CCW, counterclockwise; TS, triceps surae; TA, tibialis anterior; SCA6, spinocerebellar ataxia type 6; HC, healthy control.

### TABLE 3. Within-subject response direction variability (angular deviation, degrees) measured from single trials of upper trunk displacement

<table>
<thead>
<tr>
<th></th>
<th>GVS</th>
<th>MVS</th>
<th>VIB</th>
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<tbody>
<tr>
<td></td>
<td>R+</td>
<td>L+</td>
<td>CW</td>
</tr>
<tr>
<td>SCA6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>15</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Mean (°)</td>
<td>31.38</td>
<td>42.31</td>
<td>32.42</td>
</tr>
<tr>
<td>SD</td>
<td>16.84</td>
<td>20.69</td>
<td>15.46</td>
</tr>
<tr>
<td>Median</td>
<td>24.75</td>
<td>49.64</td>
<td>30.69</td>
</tr>
<tr>
<td>Interquartile</td>
<td>28.90</td>
<td>33.40</td>
<td>23.12</td>
</tr>
<tr>
<td>HC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Mean (°)</td>
<td>26.63</td>
<td>26.48</td>
<td>42.89</td>
</tr>
<tr>
<td>SD</td>
<td>17.34</td>
<td>15.08</td>
<td>16.49</td>
</tr>
<tr>
<td>Median</td>
<td>22.53</td>
<td>22.11</td>
<td>43.13</td>
</tr>
<tr>
<td>Interquartile</td>
<td>16.07</td>
<td>19.60</td>
<td>18.91</td>
</tr>
<tr>
<td>SCA6 vs HC</td>
<td>P</td>
<td>0.446</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Notes: One SCA6 subject did not contribute GVS responses because of technical failure. Angular deviations compared using two-tailed Mann-Whitney test. P denotes probability, with significance set at P < 0.01.

GVS, galvanic vestibular stimulation; MVS, moving visual scene; VIB, muscle vibration; R+, anode right; L+, anode left; CW, clockwise; CCW, counterclockwise; TS, triceps surae; TA, tibialis anterior; SCA6, spinocerebellar ataxia type 6; HC, healthy control.
requires a mechanism to extract the self-motion component for balance control; vestibular and proprioceptive inputs do not require this because they directly signal changes in body state.

An alternative explanation is that the enlarged visuomotor response is a direct result of abnormal cerebellar processing of visual input. The cerebellum receives retinal information indirectly from the accessory optic system and cortically processed visual information via the pons. Disturbed visual processing has been implicated in other aspects of cerebellar function. Stein suggested that the cerebellum may play an important role in the visual guidance of movement, whereas some abnormal aspects of limb-movement trajectories in cerebellar disease have been attributed to aberrant motor responses to visual information.

A third possibility is that the over-scaling results from an indirect visual disruption caused by poor oculomotor control. This could occur if retinal signals are distorted by the abnormal eye movements that were clinically detectable in all of the SCA6 patients studied here.

Some caution is required when interpreting the lack of disruption to coordinate transformation processes. A deficit in spatial transformation of information from the sensory organs’ coordinate frame to an effectors’ frame would have resulted in detectable direction errors or increased direction variability. However, in this experiment, the spatial relationship between the stimulated sense organs and the body remained fixed throughout testing. A more rigorous test of this process would involve a greater variety of postural changes, for example, by studying a range of head and trunk positions with respect to the feet rather than just the one.

**Can the Visuomotor Disturbance Cause Balance Instability?**

One hypothesis for SCA6 balance impairment is that it results from a pure motor disruption, for example, dyssynergia or muscle activation timing problems. Can an exaggerated visually evoked balance response provide the basis for an alternative sensory hypothesis for balance instability? The neuro-mechanical system controlling upright stance is often modeled as a mechanical inverted pendulum under sensory feedback control.

One way such a system could go unstable is if the gain of the feedback loops were set too high. The current results could be interpreted as reflecting an excessively high gain of the visual channel without a compensatory decrease in gain of the vestibular and proprioceptive channels, and so is compatible with this hypothesis. However, a simple objection is that cerebellar patients typically become even more unstable when deprived of vision. Nonetheless, the concept of instability through high feedback gains remains a possibility. This could occur because the relative gains of the different sensory channels are not fixed. If a sensory channel becomes unavailable, then the gains of the remaining sensory sources may be automatically increased. The cerebellum has been proposed to play a key role in adaptive gain control, at least for the vestibuloocular reflex.

Some abnormal aspects of limb-movement trajectories in cerebellar disease have been attributed to aberrant motor responses to visual information.

**Clinical Implications**

The increased gain of the visuomotor feedback loop for balance shown here may be related to the problems encountered by SCA6 patients in daily life. They often report that balance difficulties are particularly severe in busy visual environments, for instance, when walking alongside a busy road or in a crowd. Whatever the cause of the visuomotor disruption in SCA6, it opens an opportunity for targeted rehabilitation of their balance impairment. This could involve training of the oculomotor response or desensitisation training to respond more appropriately to potentially destabilizing moving visual cues in the environment.

**Acknowledgments:** We thank all of the SCA6 patients and healthy volunteers who participated in this study. The study was funded by Ataxia UK and the Medical Research Council (G0501740). P.G. works at University College London Hospitals/University College London, which receives a proportion of its funding from the Department of Health’s National Institute for Health Research Biomedical Research Centres funding scheme.

**References**


Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.