Alexander’s Law Revisited

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Submitted 15 January 2008; accepted in final form 29 April 2008

Jeffcoat B, Shelukhin A, Fong A, Mustain W, Zhou W. Alexander’s Law revisited. J Neurophysiol 100: 154–159, 2008. First published April 30, 2008; doi:10.1152/jn.00055.2008. Alexander’s Law states that the slow-phase velocity of the nystagmus caused by unilateral vestibular lesion increases with gaze in the beat direction. Two studies have shown that this gaze effect is generalized to the nystagmus caused by unilateral cold water irrigation. This indicates that the gaze effect is not the result of central changes associated with a peripheral lesion but rather because of unilateral vestibular peripheral inhibition. In this study, we show that there is a similar gaze effect on the nystagmus produced by unilateral warm water ear irrigation. Furthermore, we examined the two hypotheses of Alexander’s Law proposed in the two studies. One hypothesis is based on the gaze-dependent modulation of the vestibulo-ocular reflex (VOR) response to unbalanced canal input. The other hypothesis, however, is based on the leaky neural integrator caused by unilateral vestibular peripheral inhibition. These two hypotheses predict the same gaze effect on the nystagmus produced by cold water irrigation, but opposite gaze effects on the nystagmus produced by warm water irrigation. Our results support the first hypothesis and suggest that the second hypothesis needs to be modified.

INTRODUCTION

In 1912, Gustav Alexander discovered that the slow-phase velocity (SPV) of the spontaneous vestibular nystagmus increases as gaze moves in the direction of the fast phase and decreases as gaze moves away from the direction of the fast phase (for review, see Baloh 2002). This effect of gaze on vestibular nystagmus later became known as Alexander’s Law. Despite widespread recognition and application of Alexander’s Law by physicians, little was known about the underlying neural mechanisms until >60 yr later. In 1982 and again in 1984, Doslak et al. and Robinson et al., respectively, attempted to determine whether the observed gaze effect was from the direct unilateral inhibition caused by a peripheral lesion or from central adaptation that is induced by the peripheral lesion over a period of time. Both studies quantitatively showed a gaze effect on nystagmus evoked by unilateral cold water irrigation in normal human subjects, indicating that unilateral vestibular peripheral inhibition alone is adequate to elicit the gaze effect of Alexander’s Law.

Doslak et al. (1982) and Robinson et al. (1984) proposed different mechanisms to account for the gaze effects noted. Robinson et al. (1984) suggested that two components make up the slow phase of the nystagmus resulting from unilateral vestibular inhibition. The first component is the direct response of the vestibulo-ocular reflex (VOR) pathways to the unbalanced canal input, and this component is assumed to be independent of gaze (Fig. 1A, gray line with a slope of 0). The second component is gaze-evoked nystagmus from the effect of unilateral peripheral inhibition on the velocity to position neural integrator. This second component has been shown to be linearly dependent on gaze on nystagmus (Fig. 1A, thin black line with a negative slope) (Cannon and Robinson 1987). The observed SPV is the linear summation of the two components, which exhibits the same linear dependence on gaze as the gaze-evoked nystagmus (Fig. 1A, thick black line with the same negative slope of the thin black line). Doslak et al. (1982), however, suggested that unilateral peripheral inhibition has no effect on the neural integrator (Fig. 1B, the zero thin black line) and that the VOR pathway response to the unbalanced canal input is directly modulated by gaze (Fig. 1B, gray line with a negative slope, which is superimposed with the thick black line). Although these two hypotheses are very different, both of them can account for the gaze effect on nystagmus produced by cold water irrigation (Fig. 1A and B, thick black lines with negative slopes). Robinson et al. (1984) made an attempt to differentiate the two hypotheses by examining the curvature of the slow-phase nystagmus following unilateral vestibular inhibition. A curved slow phase would indicate a leaky integrator, consistent with the hypothesis of Robinson et al. A straight slow phase would indicate an intact integrator, which is consistent with the hypothesis of Doslak et al. The analysis of Robinson et al. showed that the curvature caused by the leaky integrator was too small to be detected in their paradigms.

Whereas both hypotheses predict the same gaze effect on nystagmus evoked by cold water irrigation, they predict opposite effects on nystagmus produced by warm water irrigation. The hypothesis of Doslak et al. predicts a positive gaze effect on the SPV (Fig. 1D, thick black line with a positive slope), but the hypothesis of Robinson et al. still predicts a negative gaze effect on the slow phase velocity (Fig. 1C, thick black line with a negative slope). The objective of this study was to examine the gaze effects on nystagmus produced by unilateral warm water irrigation and thus to differentiate the two hypotheses.

METHODS

Six normal subjects (all men; age range, 23–48 yr) gave their informed consent to participate in this study. The Institutional Review Board at the University of Mississippi Medical Center approved the experimental protocol. All subjects were free from disease, and none were taking any medication at the time of the experiments.

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Each subject underwent 2 days of testing, including 1 day for warm water irrigation (44°C at a rate of 300 ml/min) and 1 day for cold water irrigation (25°C at a rate of 300 ml/min). During a test, the subject sat comfortably with the head stabilized using a chinrest. The Chronos eye tracker head unit was worn by the subject and adjusted such that both pupils were centrally located on the video inlay of the acquisition software (Clarke 1998). During a test, the subject sat comfortably upright with the head stabilized using a chinrest. Because of the nature of the eye tracker, the subject was unable to be positioned 30° from prone as has become standard with caloric testing. Calibration of the eye tracker was performed by asking subjects fixate on targets at known locations (center and 10° from the center in left, right, up, and down directions) (Clarke 1998). Following calibration, the subject was in total darkness to prevent visual inhibition of the nystagmus. Cold or warm water irrigation was begun in one ear canal using an open loop water caloric stimulation system (GN Otometrics NCI-480). The irrigation was carried out for 2.5 min to reach a steady-state slow-phase nystagmus rate.

**FIG. 1.** The 2 current hypotheses on Alexander’s Law and their predictions on the slow-phase velocity (SPV)-gaze relationships during cold (A and B) and warm (C–F) water irrigation.
Doslak et al. 1982). The subject was asked to direct his eyes in a series of eye positions (center, 10° left, and 10° right), which were aided by a brief pulse (0.5 s) of light at each position. The sequence was repeated four times.

Images of both eyes were acquired at 100 Hz. Binocular horizontal and vertical eye position signals were calculated off-line using IRIS tracker software with a resolution better than 0.05°. The positive eye position values were referred to as right gaze and negative eye position values were referred to as left gaze. The SPV was calculated for each slow phase using linear regression (SigmaPlot; Fig. 2A). Alexander’s Law was evaluated by computing the slope of the linear regression of the SPV and the averaged eye position of the slow phase. Each regression included ≥30 slow phases during steady-state caloric irrigation. The conjugacy of the slow phase was evaluated by computing the slope of the linear regression of the left eye SPV and the right eye SPV.

RESULTS

Figure 2A shows representative binocular horizontal eye position records of the nystagmus evoked by warm water caloric irrigation (Fig. 2A, subject 4, right ear) or cold water caloric irrigation (Fig. 2C, subject 4, left ear). Note that the nystagmus beat in the opposite direction of the stimulated ear during warm water irrigation (Fig. 2A) and beat in the same direction of the stimulated ear in cold water irrigation (Fig. 2C). Figure 2, B and D, further show that the SPV varied with eye position differently under each condition. As the subject gazed in the opposite direction of the stimulated ear, the SPV increased in the warm water irrigation condition (Fig. 2B) but decreased in the cold water irrigation condition (Fig. 2D). The slope of the linear regression for the SPV and eye position was used to quantify this gaze effect. For subject 4, the regression had positive slopes during warm water irrigation (Fig. 2B, SLOPE ipsi eye = 0.19 ± 0.03 °/s°, SLOPE contra eye = 0.17 ± 0.03 °/s°, P < 0.01) and negative slopes during cold water irrigation condition (SLOPE ipsi eye = −0.09 ± 0.04 °/s°, SLOPE contra eye = −0.11 ± 0.04 °/s°, P < 0.02). Similar results were obtained for the group of subjects (n = 6), which are summarized in Fig. 3 and Table 1.

On average, there was a significant positive slope for each eye position signal of the left and right eyes (slope (left eye) = 0.17 ± 0.04 R=0.70, p <0.001 and slope (right eye) = 0.19 ± 0.03 R=0.81, p <0.001). The positive slope for the left eye was significantly greater than the positive slope for the right eye (p < 0.001). The negative slope for the left eye was significantly less than the negative slope for the right eye (p < 0.01). The SPV was calculated for each slow phase using linear regression (inset plots in A). Alexander’s Law was examined by computing the slopes of the regression lines for the SPV and eye position (B, warm water irrigation; D, cold water irrigation).

FIG. 2. Sample of warm water and cold water irrigation-induced nystagmus (subject 4). Position signals of the left (black) and right (gray) eyes were plotted as a function of time during steady-state irrigation (A, warm water irrigation, right ear; C, cold water irrigation, left ear). The beat direction of the nystagmus is to the ipsilateral direction in A and to the contralateral direction in C. SPV was calculated for each eye using linear regression (inset plots in A). Alexander’s Law was examined by computing the slopes of the regression lines for the SPV and eye position (B, warm water irrigation; D, cold water irrigation).
during warm water irrigation (SLOPE\textsubscript{ipsi\_eye} = 0.22 ± 0.08 °/s°, SLOPE\textsubscript{contra\_eye} = 0.18 ± 0.04 °/s°, \( P < 0.05 \)) and a significant negative slope for each eye during cold water irrigation (SLOPE\textsubscript{ipsi\_eye} = −0.12 ± 0.05 °/s°, SLOPE\textsubscript{contra\_eye} = −0.08 ± 0.02 °/s°, \( P < 0.05 \)).

To assess the conjugacy of the slow phase component, we computed the slope of linear regression for the ipsilateral eye SPV and the contralateral eye SPV, i.e., the conjugacy index (Fig. 4A). On average, the conjugacy index was 1.12 ± 0.03 and 0.95 ± 0.02 during cold or warm water irrigation, respectively (Fig. 4B).

**DISCUSSION**

To our knowledge, this is the first study that examined Alexander’s Law using unilateral vestibular peripheral excitation (i.e., warm water irrigation). We found that Alexander’s Law, in its current form, holds true only for the nystagmus resulting from unilateral vestibular inhibition (e.g., cold water irrigation, unilateral vestibular peripheral lesion, etc.) and not for the nystagmus resulting from unilateral vestibular peripheral excitation (e.g., warm water irrigation, unilateral vestibular peripheral viral infection, etc.). For nystagmus resulting from unilateral vestibular inhibition, the SPV increases with the gaze in the beat direction as stated by Alexander’s Law (Fig. 2, C and D). For nystagmus resulting from unilateral vestibular excitation, however, the SPV increases with gaze in the direction opposite to the beat direction (Fig. 2, A and B). These results challenge both the current form of Alexander’s Law and the leaky neural integrator hypothesis of the gaze effect of Robinson et al. (1984).

Recently, we studied effects of gaze on abducens neuron responses to a brief unilateral vestibular stimulation in behaving monkeys (Zhou et al. 2004, 2005, 2007). We found that the evoked neuronal responses by the same unilateral vestibular

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**TABLE 1. Statistic summary of the regressions for slow phase velocity and eye position**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Eye</th>
<th>Cold Water Irrigation</th>
<th>Warm Water Irrigation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope (°/s°)</td>
<td>( R )</td>
<td>( P &lt; 0.05? )</td>
</tr>
<tr>
<td>Subject 1</td>
<td>Ipsi</td>
<td>−0.33</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>Contra</td>
<td>−0.15</td>
<td>0.40</td>
</tr>
<tr>
<td>Subject 2</td>
<td>Ipsi E</td>
<td>−0.05</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Contra</td>
<td>−0.06</td>
<td>0.53</td>
</tr>
<tr>
<td>Subject 3</td>
<td>Ipsi E</td>
<td>−0.04</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>Contra</td>
<td>−0.04</td>
<td>0.52</td>
</tr>
<tr>
<td>Subject 4</td>
<td>Ipsi E</td>
<td>−0.09</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>Contra</td>
<td>−0.11</td>
<td>0.50</td>
</tr>
<tr>
<td>Subject 5</td>
<td>Ipsi</td>
<td>−0.16</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>Contra</td>
<td>−0.10</td>
<td>0.24</td>
</tr>
<tr>
<td>Subject 6</td>
<td>Ipsi</td>
<td>−0.02</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Contra</td>
<td>−0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>Ipsi</td>
<td>−0.12 ± 0.05</td>
<td>0.43 ± 0.09</td>
</tr>
<tr>
<td></td>
<td>Contra</td>
<td>−0.08 ± 0.02</td>
<td>0.37 ± 0.09</td>
</tr>
</tbody>
</table>
stimulation is linearly related to gaze, indicating that the interaction of vestibular signal and gaze signal is multiplicative rather than being additive as presently assumed. The multiplicative interaction may be implemented either at the stage that converts presynaptic spike trains into postsynaptic currents or at the stage that converts the effective synaptic currents reaching the soma into action potentials (du Lac 1996). Based on these new results, we extended the hypothesis of Doslak et al. (1982) and propose a new hypothesis that accounts for the gaze effects observed in both cold and warm water irrigation conditions. In the new hypothesis, the sensitivity of extraocular motoneurons to inputs is not fixed but varies with gaze. When the right horizontal canal is activated (e.g., warm water irrigation in the right ear), there is an increase in the firing rate of the left abducens neurons, which increases with leftward gaze. Thus the VOR response is in the left direction and its amplitude is increased when gaze moves in the same direction, i.e., the linear regression of VOR response and gaze has a positive slope (Fig. 1D). When the right horizontal canal is inactivated (e.g., cold water irrigation in the right ear), there is a decrease in the firing rate of the left abducens neurons, which also increases with leftward gaze. Thus the VOR response is in the right direction and its amplitude is increased as gaze moves to the left direction, i.e., the linear regression of VOR response and gaze has a negative slope (Fig. 1B).

Although the new hypothesis proposed here provides a simple interpretation of the data, the abnormal neural integrator hypothesis cannot be ruled out. For example, the positive SPV-gaze regression slope observed during warm water irrigation can be accounted for if unilateral vestibular excitation results in an unstable neural integrator (Fig. 1E) instead of a leaky neural integrator as originally proposed (Zee et al. 1981). The current paradigm, however, cannot directly assess the status of the neural integrator during unilateral vestibular excitation and inhibition. It may be possible that both the gaze-dependent motoneuron excitability and the abnormal neural integrator contribute to the effects of gaze on the nystagmus induced by unilateral vestibular stimulation (Fig. 1F).

In this study, we also examined the conjugacy of the nystagmus induced by single labyrinth excitation and inhibition using warm and cold water ear irrigation, respectively. We found that the nystagmus produced by unilateral caloric irrigation was primarily conjugate (Fig. 4B). These results indicate that the net innervations received by the two eyes were roughly equal despite the fact that the anatomical projections from a single labyrinth to the two eyes are not symmetrical (Baker and Highstein 1978). This conclusion, however, may not be generalized to other conditions for two reasons. First, caloric irrigation is a low frequency stimulation of 0.003 Hz (Hamid et al. 1987). Vestibular nystagmus may become very disjunctive if it is produced by high-frequency stimulations (e.g., head impulses). Second, there is considerable individual variability in the nystagmus conjugacy in the present study. For example, subjects 1 and 2 showed more disconjugacy than others. Given the limited data, it is difficult to determine the factors that contribute to the individual variability. It is possible that this individual variability may be even larger when other stimulations are used. This issue needs to be further examined in future studies.

ACKNOWLEDGMENTS
We thank D. Thielemann for help during the project.
REFERENCES


