Published in final edited form as:

Ann N Y Acad Sci. 2011 September ; 1233(1): 155–161. doi:10.1111/j.1749-6632.2011.06119.x.

Critical role of cerebellar fastigial nucleus in programming sequences of saccades

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Abstract

The cerebellum plays an important role in programming accurate saccades. Cerebellar lesions affecting the ocular motor region of the fastigial nucleus (FOR) cause saccadic hypermetria; however, if a second target is presented before a saccade can be initiated (double-step paradigm), saccade hypermetria may be decreased. We tested the hypothesis that the cerebellum, especially FOR, plays a pivotal role in programming sequences of saccades. We studied patients with saccadic hypermetria due either to genetic cerebellar ataxia or surgical lesions affecting FOR and confirmed that the gain of initial saccades made to double-step stimuli was reduced compared with the gain of saccades to single target jumps. Based on measurements of the intersaccadic interval, we found that the ability to perform parallel processing of saccades was reduced or absent in all of our patients with cerebellar disease. Our results support the crucial role of the cerebellum, especially FOR, in programming sequences of saccades.

Keywords

fastigial nucleus; double-step; saccade; latency; spinocerebellar ataxia; hypermetria; parallel processing

Introduction

In a prior study,¹ we showed that in response to the rapid presentation of a sequence of two visual stimuli (double-step paradigm), cerebellar patients showed greater inaccuracy of their first saccade compared to saccades made to single target jumps. Moreover, cerebellar patients often failed to make a saccade to the first target jump. Thus, it seemed that presentation of a second target jump confounded the ability of cerebellar patients to respond to the first stimulus. Control subjects also showed greater inaccuracy for double versus single target jumps, but errors of initial saccades to double-step stimuli were significantly greater in cerebellar patients. In that study, we noted that two patients with a recessive form of ataxia (SCASI),² who showed marked saccadic hypermetria to single target jumps, often made less hypermetric initial saccades to double-step stimuli (Fig. 1).

The dorsal vermis and the caudal fastigial ocular motor region (FOR) to which it projects play important roles in making saccades accurate. In addition to signals from Purkinje cells in the dorsal vermis, the FOR receives inputs from pontine nuclei via the mossy fibers.³ Studies in macaques employing electrophysiological and pharmacological inactivation of FOR indicate that this nucleus plays a pivotal role in determining the beginning and end of saccades.^{4,5} One hypothesis is that early discharge of one FOR promotes the onset of

contralaterally directed saccades, and later discharge in the other FOR ends the eye movement.^{6,7} Electrophysiological evidence indicates that populations of Purkinje cells in the dorsal vermis send a saccadic “stop signal” to the FOR.⁸ Thus, it follows that hypermetria could arise if the Purkinje cell stop signal arrived late or if the FOR failed to discharge on time. To test this hypothesis, we studied changes in saccadic gain during a double-step task in which the interval between presentation of the first and second target was systematically varied. We restudied our two SCASI patients, and, since the location of the cerebellar dysfunction that accounts for their severe saccadic hypermetria is unknown,⁹ we also studied two patients with surgical lesions that included the FOR^{10,11} and four healthy control subjects.

We also considered the effect of lesions of the cerebellum on the temporal programming of saccadic responses to the first and second target jumps in the double-step task (Fig. 2). Early studies concluded that the saccadic system was a serial processor, such that saccade processing for the second target jump only started after the first saccade was complete.^{12,13} However, more recent work demonstrated that parallel processing occurs during responses to double-step stimuli such that if the delay period between the second target jump and initial saccade is longer, then the intersaccadic interval will be shorter (rather than serial processing, in which the intersaccadic interval would be fixed—see Fig. 2).^{14,15} Using this approach, we asked whether parallel processing of saccades was still present in our patients with cerebellar disease.

Methods

Subjects

We studied four patients with evidence of cerebellar disease (three male and one female; age range 59–62 years, mean = 60.5); two diagnosed with SCASI² and two with FOR lesions, following surgery for midline cerebellar cystic astrocytoma tumors.^{10,11} All cerebellar patients underwent a formal neurological evaluation prior to selection; all had normal mental status and clearly understood the nature of the testing. We also tested four healthy control subjects (four male; age range 29–64 years, mean = 42.5). All individuals gave signed, informed consent in accordance with our Institutional Review Board and the Declaration of Helsinki. Testing took place in a dark room, and an investigator remained in the room and encouraged all subjects during the session. Full methodological details are described elsewhere.¹

Experimental methods, stimuli, and paradigms

We measured horizontal and vertical eye movements using the magnetic search coil technique.¹ During testing, subjects were seated in a stationary chair with a headrest to restrain movement. Subjects viewed targets projected onto a tangent screen at a viewing distance of 1.2 m. We tested saccades to 280 randomly interleaved visually guided single-step (SS, 60% of stimuli) and double-step (DS, 40% of stimuli) target jumps (Fig. 3). Each trial started as subjects viewed a central green target. After two seconds, the fixation target went out and a red target (T1) immediately appeared at one of four locations horizontal from the fixation target ($-10^\circ, -5^\circ, 5^\circ, 10^\circ$ from center). For SS trials, T1 remained on for two seconds, but for DS trials T1 was present for one of five possible durations (80, 90, 100, 120, 140 ms interstimulus intervals) before a second target (T2) appeared in one of the remaining three locations (*e.g.*, if T1 = 10° , then T2 could be $5^\circ, -5^\circ$, or -10°). Subjects were instructed to look at the targets as they appeared; they were not instructed to cancel the initial saccade to the first target of double-step stimuli,¹⁶ since we sought to promote a mental state similar to that during normal activities.

Data analysis

We sorted saccadic responses into categories, each with single-step (SS), first target of double-step (DS1), and second target of double-step (DS2) trial types for comparison. We further separated DS1 trials in two ways: based on whether T2 appeared in the opposite direction or same direction from T1 and based on T1 duration (interstimulus interval).

We computed the horizontal components of saccadic gain (initial eye displacement/ target displacement) for single-steps and both components of double-steps.¹ We also measured the latency to onset of each saccadic response (time of saccade onset – time of stimulus onset). Using these latencies, we were able to compute delay period and intersaccadic interval, as summarized in Figure 2.

Our primary analysis was between pooled data from the two groups of cerebellar patients (SCASI and FOR) and normal subjects; for this we used the Mann–Whitney Rank Sum Test since data were not normal in distribution. We also compared each cerebellar patient's double-step data set against the corresponding data from single-step target jumps using Kruskal–Wallis One-Way ANOVA on Ranks with 5 degrees of freedom (Dunn's Method for pair-wise comparisons). Correlations were checked with the Pearson Product Moment Correlation test. Unless otherwise specified, statistical significance corresponded to $P < 0.05$.

Results

Gain

Figure 4A–C summarizes pooled results from all control subjects, SCASI patients, and FOR patients in which the second stimuli of the double-step appeared opposite in direction from the first (and into the opposite hemifield). For control subjects (Fig. 4A), the gain values of initial saccades made to double-step stimuli decreased as the interstimulus interval decreased (correlation $P < 0.05$). The gain of saccades made to double-step target jumps (DS1) for interstimulus intervals of 80 ms and 90 ms were statistically smaller than single-step gains. For SCASI and FOR patients, gain values of the initial saccade to a double-step stimulus were generally smaller than gain values of saccades made to single target jumps. However, there were no significant correlations between decreasing interstimulus interval and gain. In SCASI patients (Fig. 4B), the initial saccade gain values for interstimulus intervals of 90–140ms were statistically smaller than the gain of saccades made to single target jumps (*e.g.*, mean SS gain = 2.24; for interstimulus interval of 90ms, mean DS1 gain = 1.82). Furthermore, in FOR patients (Fig. 4C), initial saccades made to 90ms and 100ms DS1 stimuli were statistically smaller than saccades to single target jumps (*e.g.* mean SS gain = 0.96; for interstimulus interval of 90ms, mean DS1 = 0.713). Thus, double-step stimuli decreased the gain of initial saccades compared with the saccades to single-step stimuli in both SCASI and FOR patients.

Additionally, SCASI and FOR patients failed to make any saccade at all to the first target of a double-step stimulus (with second target in the opposite direction) more often than controls did (SCASI: 51% of trials; FOR: 40%; controls: 29%).

Latency

As noted in the Introduction, our goal was to determine whether there was an inverse relationship between the intersaccadic interval and the delay period between the second target jump and the initial response since this has been shown to be a reliable index of parallel processing of saccades (Fig. 2).^{14,15} Figure 4D–F summarizes the results. Normal subjects' latency data (A) showed a clear inverse relationship between delay period and

intersaccadic interval with a slope of -0.7 . However, both SCASI patients (E) and FOR patients (F) showed smaller negative slopes (-0.13). When we calculated the correlation coefficient for each set of latency data, we found a significant correlation between intersaccadic interval and delay for normal subjects ($P < 0.05$) but not for SCASI or FOR patients. These results indicate that the cerebellar patients had difficulty parallel processing double-step stimuli.

Discussion

We set out to test the hypothesis that the cerebellar fastigial nucleus acts as a functional bottleneck for programming sequences of saccades. Our prior study had raised this possibility when we observed that certain cerebellar patients (those with SCASI)² would overshoot single target jumps but at times make less hypermetric initial saccades to double-step stimuli (Fig. 1).¹ Our hypothesis, based on the concept of governance of the brainstem push-pull control of saccades by FOR,^{6,7,17} predicted that a critically timed and oppositely directed second target jump might terminate an ongoing initial saccade in SCASI patients, making it less hypermetric, and that this effect would be a function of the interstimulus interval. Conversely, patients with lesions involving the FOR would not be expected to show such a correlation between interstimulus interval and saccade amplitude, lacking any governance of saccadic burst neuron firing by the FOR. We also measured the latency of saccades to double-step stimuli to look for evidence of parallel processing.

We found that both patients and normal subjects showed lower gain values of the initial saccade to double-step stimuli compared with responses to single target jumps (Fig. 4A–C). For both normal subjects and FOR patients, the smallest mean gain values tended to occur with the shorter interstimulus intervals.

Our second finding was that, using currently accepted methods,^{14,15} normal subjects showed evidence of parallel processing of saccades, but SCASI patients and patients with FOR lesions did not (Figure 4D–F). Taken together, these findings support our proposal that the cerebellar circuits, especially those involving the fastigial nucleus, are important for parallel processing of saccades. However, a different mechanism from the one we proposed must be invoked to account for why initial saccades are smaller when second targets are presented. One possibility is that this behavior was due to the superior colliculus, which sends projections to brainstem omnipause neurons¹⁸ that could then terminate a saccade by inhibiting brainstem burst neurons.¹⁹ Since omnipause neurons are silent during blinks as well as combined saccade-vergence movements,¹⁷ it might be possible to investigate further the mechanisms that terminate saccades in patients with lesions involving the fastigial nucleus.

Prior experiments have shown that parallel processing of saccades relies heavily on circuits between cerebral cortex and thalamic nuclei.²⁰ Our study shows that such studies rest on the assumption that the cerebellar connections with the fastigial nucleus are functioning normally, which is usually the case. However, if there is coexistent cerebellar disease, then deductions about cortical processing of saccades may be confounded by the independent effects of the cerebellum on parallel processing.

Conclusions and clinical implications

Do our findings generalize beyond the control of eye movements? In the clinical setting, cerebellar patients have difficulty responding appropriately to changing environmental visual stimuli, often increasing their risk of falling.²¹ We have shown that the cerebellum is important for programming of saccades when visual stimuli abruptly change. We propose

that studying the effects of cerebellar disease on the programming of sequences of saccades provides an index of how well the cerebellum contributes to parallel processing of neural commands in general. Thus, it seems likely that other cerebellar circuits concerned with rapid programming of limb movements and gait might be similarly compromised. In general, our findings suggest that the impaired ability of cerebellar patients to cope with unexpected environmental changes may be due to an inability to process neural commands in parallel.

Acknowledgments

Supported by National Institutes of Health grant R01 EY06717, the Department of Veterans Affairs, and the Evenor Armington Fund (to Dr. Leigh).

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Figure 1.

Representative eye movement records of a control subject and a SCASI patient showing responses to single- and double-step target jumps. The control subject slightly undershoots (saccade gain = 0.95) the single-step stimulus (A) and makes a more hypometric saccade (gain = 0.87) in response to the double-step stimulus (B). The SCASI patient makes a very hypermetric saccade to the single target jump (gain = 1.71), but overshoots much less with his initial response to the double-step jump (gain = 1.11).

Figure 2.

Diagram of an analytic method for determining whether the brain programs initial saccadic responses to double-step stimuli serially (processing of saccade to the second step begins after the first response is complete and corresponds to the intersaccadic interval—ISI) or in parallel, in which case processing starts as soon as the second target step occurs. By changing the interstimulus interval, it is possible to induce changes in the “delay” period between the appearance of the second target and the onset of the first saccadic response. Graphs at right show that in serial processing of saccades, the ISI will be constant irrespective of the delay period, but, in parallel processing, ISI is inversely related to the delay period.¹⁴

Figure 3.

Single-step and double-step paradigms in which green circles represent the center fixation LED, red circles represent the laser target, partial circles represent the location of the previous target, solid arrows represent the saccade path, and dotted arrows represent the previous saccade path to the initial target location. DS T1 is the first double-step target location. The possible double-step second target (DS T2) locations are numbered by whether the saccade to DS T2 is made (1) opposite in direction from initial saccade and into the opposite hemifield; (2) opposite in direction from initial saccade but remains in the same hemifield; or (3) in the same direction as the initial saccade and remains in the same hemifield (e.g. DS T1 = -5° , DS T2 = -10°).

Figure 4.

(A–C) Boxplot summary (with percentiles) of gain values for initial saccades made to double-step (DS) stimuli as a function of the interstimulus interval (from .08–.14 seconds). The leftmost boxplot (cross-hatched) of each subject are single-step (SS) gain data. Asterisks indicate when responses to DS are significantly different from SS responses. Normal subjects' gain data were positively correlated with interstimulus interval; however, cerebellar patients' data were not. (D–F) Scatter plots as evidence for parallel processing of saccades (indicated by presence of negative slope). ISI (intersaccadic interval) and delay period are defined in Figure 2. Only normal subjects showed a significant correlation (negative slope) between ISI and delay period. Normal subjects' data are shown on top (A

and D), SCASI patients' data are in the middle (B and E), and FOR patients' data are on the bottom (C and F).