Saccade Adaptation in Williams-Beuren Syndrome

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METHODS. Saccade amplitude modification was elicited by backward steps (30% of target eccentricity) during the primary saccade in a classic saccade-adaptation paradigm.

RESULTS. Patients with WBS showed a significant decrease in saccade amplitude. Furthermore, we observed that higher saccade accuracy before adaptation was related to more adaptation.

CONCLUSIONS. The increased variability in motor performance does not abolish the ability for saccadic adaptation in subjects with WBS. Our results are congruent with the notion that part of the behavioral deficits observed in WBS may have a cerebellar origin.

Saccade eye movements (or saccades) are fast rotations of the eye which can change the point of regard rapidly from one position in space to another. Saccades are ballistic eye movements that are generally very accurate, having an amplitude of approximately 90% to 95% of the target amplitude (saccadic undershoot) to minimize saccadic duration. Moreover, inaccurate voluntary visually guided saccades are warranted as they hamper adequate processing of the visual environment. Therefore, the oculomotor system monitors saccadic accuracy, and after an inaccurate saccade, it tries to modify the amplitude of subsequent saccades of the same amplitude and direction. This modification process is commonly regarded as a form of motor learning in which the cerebellum plays a crucial role. The modification process is widely studied in the laboratory by means of a so-called saccade adaptation paradigm (for a review, see Ref. 4). In the saccade adaptation paradigm, the visual target of a saccade is displaced during the saccade toward it. Because vision is impaired during the fast saccadic eye movement, the sudden change in position is unnoticed. Only after the saccade has reached its end position is the oculomotor system able to register the error between the (new) target position and the saccade end point. Changing the target position consistently during several trials leads to a gradual change in saccadic amplitudes in healthy humans, to minimize this recurrent mismatch between post-saccadic target position and saccadic end points.

In a previous study, we showed that the eye movement behavior of patients with Williams-Beuren Syndrome (WBS) is disturbed, showing a significant degree of saccade dysmetria. WBS, also known as Williams syndrome (OMIM database 194050; Online Mendelian Inheritance in Man; http://www.ncbi.nlm.nih.gov/Omim; provided in the public domain by the National Center for Biotechnology Information, Bethesda, MD) is a rare genetic neurodevelopmental disorder, characterized by several distinctive medical, behavioral, and cognitive deficits caused by a microdeletion on chromosome 7, in region q11.23 (for reviews see, Refs. 8,9–11). Patients with WBS have several marked features, such as mental retardation, dysmorphic facial features, supravalvar aortic stenosis and transient infantile hypercalcemia. Furthermore, a specific cognitive profile is often observed in WBS with relatively preserved verbal and visual recall skills, but moderate to severe impairments in visuospatial tasks, such as block copying,14–16 drawing,17 and depth processing.18

Many individuals with WBS, especially children, show mild disturbances in motor behavior.19,20 The observed saccade dysmetria,7 as well as several other studies,21,22 implicate a role for the cerebellum in part of the behavior of these patients, although WBS is generally not regarded as a typical cerebellar syndrome.

In the present study, we extended the notion of cerebellar deficits in WBS by looking into the learning process of saccadic eye movements. We investigated whether WBS patients are capable of modifying their saccadic amplitudes in a short-term saccadic adaptation paradigm, despite the saccadic dysmetria observed in normal viewing conditions.

METHODS

Subjects

For the present experiment informed consent was obtained from the parents of 24 subjects with WBS. The experiment described herein was part of a larger study on WBS and was approved by the Medical Committee of the Erasmus MC, according to the 1994 Declaration of Helsinki.

The submicroscopic deletion of genes (among which are ELN and CYLN2) in chromosome 7, band q11.23, detected by fluorescence in situ hybridization (FISH) and a screening for phenotypic characteristics associated with WBS,23 confirmed the diagnosis of WBS in all subjects (WBS group, n = 24, 10–26 years of age; low to moderate level of intelligence [IQ < 80], as estimated from school and parental reports).

A control group of children and adults without any neurologic or neuropsychological deficits was recruited through the hospital and university (CS, n = 9; 13–30 years of age; normal IQ).

All subjects had normal or corrected-to-normal visual acuity and were (apparently) without any obvious signs of oculomotor disturbances that could be seen without the aid of an eye-tracking device (e.g., normal smooth pursuit and normal gaze shifts).

Stimuli and Apparatus

The experiment took place in complete darkness. Subjects were seated 70 cm in front of a 21-in. computer screen, covered with a red filter that eliminated all light reflections of the monitor. The visual stimulus was a single small red dot (0.5° of visual angle) presented on a black
background. The subject was instructed to look at the red dot all the time.

The experiment was a classic backward saccade adaptation paradigm. It consisted of two distinct phases: between 10 and 20 baseline trials, followed by 80 adaptation trials. In both phases, each trial started with the dot being displayed at 10° of visual angle on the left side of the screen. After a random interval between 1.5 and 2 seconds, the dot was removed on the left and subsequently displayed 10° on the right side of the screen, yielding a target amplitude of 20° of visual angle. This target displacement evoked a saccadic eye movement from left to right. In the baseline trials, the dot stayed on the right side of the screen for approximately 1.5 seconds, after which the next trial was started. These trials made up the baseline. In the adaptation trials, the dot on the right stepped 6° (i.e., 30% of the target amplitude) to the left (backward) during the saccadic eye movement toward it (see Fig. 1).

Monocular eye position was recorded using infrared video-oculography (EyeLink 2.04, SensoMotoric Instruments, Berlin, Germany) at a sample rate of 250 Hz. Head movements were restrained by means of a chin rest, and good head stability was continually checked by the experimenter using the built-in head-tracking camera of the EyeLink system. Eye position was calibrated with the built-in automatic routine. Subjects looked at the stimuli with the preferred eye as estimated by a classic eye-preference test, while the other eye was patched.

**Analysis**

Saccades were marked according to duration, amplitude, and velocity criteria. In each subject, the gains of the saccadic eye movement made in response to the target were calculated in each trial. However, sometimes the saccade was lost due to tracking problems of the EyeLink or due to simultaneous blinking of the subject. The gain was calculated as the saccadic amplitude divided by the target amplitude; and, therefore, a gain of 1 reflects a saccadic amplitude of 20°. In each subject, the mean and SD of the gains in all baseline trials were calculated. The adapted gain was taken as the average of the gains of the last 10 successfully recorded saccades made in the adaptation trials. The adaptive gain change was calculated as the difference between the adapted gain and the average baseline gain. Differences between the two groups were statistically assessed with t-tests.

**RESULTS**

The saccadic adaptation experiment was performed successfully by all subjects. Figure 2 shows the saccadic amplitudes during the experiment of two control subjects (CS) and four subjects with WBS. Regression analyses showed no systematic changes in saccadic amplitudes during the baseline trials.

Figure 3 shows the distribution of saccadic gain changes in the two groups. A significant modification of saccadic ampli-

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**FIGURE 1.** In an adaptation trial, the target at 10° on the right is shifted backward 6° during the saccadic eye movement toward it, yielding a hypermetric saccade and a subsequent correction saccade.

**FIGURE 2.** The saccadic gains versus trial numbers of two control subjects (CS 1–2) and four subjects with WBS (WBS 1–4). The first 10 to 20 trials are baseline trials (left of vertical line), followed by 80 adaptation trials.
adapted more when the baseline gains are larger. The correlation between the changes in gain and the standard deviations of the baseline gains was marginally significant ($r = 0.45, P = 0.026$), suggesting that the low variability in baseline gains allows the occurrence of a higher adaptation of saccadic amplitudes.

**Discussion**

A significant short-term saccadic adaptation was observed in a majority of WBS subjects (Fig. 5). However, the same subjects showed prominent signs of saccade dysmetria for targets that appear suddenly (Fig. 4), which is in good agreement with our previous findings when using stationary targets. Therefore, the high saccadic amplitude variability in WBS subjects does not inhibit their capacity for saccadic motor learning.

Furthermore, we also observed significant correlations between the average or variability in baseline gains and saccadic amplitude change. Normal subjects with a low saccade-to-saccade variability also seem to show the greatest ability to adapt their amplitudes. The moderate saccadic adaptation in some patients with WBS may therefore be attributable to the higher variability in saccadic amplitudes. Indeed, the patients with WBS who showed less gain changes than the least-adapting control subject, had a higher saccadic variability in the baseline trials (Fig. 5B). The saccadic eye movement of patients with WBS is similar to the saccadic behavior observed in patients with cerebellar lesions and cerebellar degeneration in which saccadic adaptation is not completely abolished, despite their greater saccade-to-saccade variability in saccadic amplitude.

Therefore, although the saccadic eye movement behavior of WBS subjects suggests that their oculomotor system is less efficient in maintaining a high level of saccadic accuracy, the present study suggests that the system still has the capacity of modifying the saccadic amplitudes when their accuracy is reduced too much. With hindsight, the forward-step adaptation paradigm (instead of the most often used backward-step paradigm) may have been more effective in evoking saccadic adaptation, because the average baseline gains in the whole WBS group are hypometric (see Fig. 4A) and a forward step would hence increase the post-saccadic errors in most patients with WBS and their saccadic inaccuracies. However, the forward-step paradigm has been found to be less effective in normal control subjects than the backward-step paradigm in eliciting saccadic amplitude changes.

The cerebellum plays a critical role in maintaining saccade accuracy. Cerebellar lesions often induce saccade dysmetria and may impair or abolish the capacity for rapid saccadic adaptation. For instance, lesions of the oculomotor vermis (OVM) in monkeys induced severe saccadic hypometria and effectively prevented the capacity for rapid adaptation. How-
ever, some learning still occurs in these monkeys, since saccadic amplitudes became less hypometric (but still quite variable) during the year after the lesioning operation.\textsuperscript{29} Saccadic dysmetria accompanied with reduced capacity of saccade adaptation has also been found in humans with cerebellar infarcts or degeneration.\textsuperscript{27,28}

We suggest that the saccadic eye movements in patients with WBS may be the result of deficits in cerebellar functioning. Several other observations support the notion that the cerebellum may be involved in WBS. First, morphologic studies of the brains of patients with WBS have shown reduced volumes of the cerebellum.\textsuperscript{52-55} Second, although they are not ataxic, individuals with WBS often have an abnormal gait and commonly show problems in descending stairs and moving over surface changes.\textsuperscript{19,20,32-34} Third, cytoplasmic linker protein II (\textit{CYLN2}) encoding CLIP-115, which is prominently expressed in cerebellar structures, is deleted in WBS.\textsuperscript{21}

It is still unclear how the short-term process of saccadic adaptation relates to maintaining saccadic accuracy in daily life. We did not investigate neurologic functioning extensively (e.g., using the International Cooperative Ataxia Rating Scale [ICARS]\textsuperscript{35}), and therefore we cannot relate the present findings to the level of cerebellar functioning in general, although none of our WBS subjects was ataxic. In this respect, it also has to be noted that WBS is not a progressive disease and that the observed neurologic symptoms do not change during life. In the present study, we did not observe any correlation between the chronological or the mental age of the WBS subjects and the ability for saccadic adaptation or saccadic variability.\textsuperscript{7} The developmental level may be important for saccadic control on a higher, more cognitive level, for instance in planning saccade scan paths during visual search tasks. Although the outcome of numerous studies points out that several brain structures (cerebellum, thalamus, and cortex) contribute significantly to the process of saccade amplitude modification,\textsuperscript{4} the learning process involved in saccadic adaptation seems to be operating on an unconscious level and does not depend on a special cognitive strategy. This is important, because several other visual impairments in cognitive strategies can be observed in WBS, such as cognitive deficits with respect to visuospatial processing as, for instance, observed in drawing, block copying, and pattern recognition\textsuperscript{8} and in depth processing.\textsuperscript{18}

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\textbf{References}


