Exp Brain Res (2005) 166: 200–209
DOI 10.1007/s00221-005-2355-1

RESEARCH ARTICLE

J. N. Van der Geest · G. C. Lagers-van Haselen
J. M. van Hagen · E. Brenner · L. C. P. Govaerts
I. F. M. de Coo · M. A. Frens

Visual depth processing in Williams–Beuren syndrome

Received: 23 July 2004 / Accepted: 14 March 2005 / Published online: 18 June 2005

Abstract Patients with Williams–Beuren Syndrome (WBS, also known as Williams Syndrome) show many problems in motor activities requiring visuo-motor integration, such as walking stairs. We tested to what extent these problems might be related to a deficit in the perception of visual depth or to problems in using this information in guiding movements. Monocular and binocular visual depth perception was tested in 33 patients with WBS. Furthermore, hand movements to a target were recorded in conditions with and without visual feedback of the position of the hand. The WBS group was compared to a group of control subjects. The WBS patients were able to perceive monocular depth cues that require global processing, but about 49% failed to show stereopsis. On average, patients with WBS moved their hand too far when no visual feedback on hand position was given. This was not so when they could see their hand. Patients with WBS are able to derive depth from complex spatial relationships between objects. However, they seem to be impaired in using depth information for guiding their movements when deprived of visual feedback. We conclude that the problems that WBS patients have with tasks such as descending stairs are not due to an inability to judge distance.

Keywords Williams–Beuren syndrome · Visual depth · Perception · Motor coordination · Sensorimotor integration

J. N. Van der Geest (✉) · G. C. Lagers-van Haselen
E. Brenner · M. A. Frens
Department of Neuroscience,
Erasmus MC, PO Box 1738,
3000 DR Rotterdam, The Netherlands
E-mail: j.vandergeest@erasmusmc.nl
Tel.: +31-10-4087059
Fax: +31-10-4089459

J. M. van Hagen
Department of Clinical Genetics and Human Genetics,
VU University Medical Center,
Amsterdam, The Netherlands

L. C. P. Govaerts
Department of Clinical Genetics,
Section Postnatal Cytogenetics, Erasmus MC,
Rotterdam, The Netherlands

I. F. M. de Coo
Department of Neurology, Erasmus MC,
Rotterdam, The Netherlands

Introduction

Williams–Beuren syndrome (WBS, also known as Williams Syndrome; OMIM database #194050, see http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=194050), is a genetically-based neurodevelopmental disorder, caused by a microdeletion on chromosome region 7q11.23 (Osborne et al. 1996; Francke 1999; Korenberg et al. 2000). The WBS patients have several marked features, such as mental retardation, dysmorphic facial features, supravalvular aortic stenosis, and transient infantile hypercalcemia (Bellugi et al. 1999; Lashkari et al. 1999). Concentration and attentional difficulties and high distractibility are common behavioral problems in WBS (Davies et al. 1998; Morris and Mervis 2000). Furthermore, a specific cognitive profile is often observed in WBS (Bellugi et al. 2000; Mervis et al. 2000), with relatively preserved verbal and visual recall skills (Udwin and Yule 1991), but moderate to severe impairments in visuo-spatial tasks, such as block copying (Atkinson et al. 2001; Farran et al. 2001; Nakamura et al. 2001) and drawing (Stiles et al. 2000). The poor performance on these tasks specifically suggests deficits in processing the global configuration of objects (Bihrle et al. 1989; Kovacs et al. 2001). For instance, when patients with WBS copy drawings, local elements and details are often correctly reproduced whilst the global configuration (the spatial relationships between the local elements) is altered or left out (Bellugi et al. 1999). The development of visual functioning is also found to be abnormal in many WBS patients, and is marked by a high incidence of, for example, strabismus, low visual acuity, and amblyopia (Atkinson et al. 2001).

Many individuals with WBS, especially children, show difficulties in motor activities involving visuo-motor integration (MacDonald and Roy 1988; Trauner et al. 1989; Chapman et al. 1996; Withers 1996), such as walking on non-uniform surfaces and descending stairs. These difficulties might be related to deficits in visual processing that hamper the proper visual guidance of one's movements. Indeed, reduced stereopsis—the sub-optimal perception of binocular depth—is likely to be found in WBS (Sadler et al. 1996; Olitsky et al. 1997; Atkinson et al. 2001). However, typically developed individuals with no or sub-optimal binocularity can still function well using only non-stereoscopic (monocular) depth cues (von Noorden 1996).

Binocular depth cues arise from the slightly different images projected onto our two eyes. Monocular depth cues, such as occlusion, perspective and motion parallax, normally also provide abundant information about the relative distances between different objects and the distance between objects and oneself. In order to extract and use such information, one has to integrate several features, such as the height of your eyes and the height of an object if you intend to step onto it.

In this paper, we investigate the processing of visual depth in patients with WBS. The noted problems in global processing in WBS might suggest that the use of relationships between visible structures to judge depth is disturbed. On the other hand, inadequate use of visual depth information for movements might also account for the difficulties encountered in motor activities requiring the integration of visual and proprioceptive information. Here we will show that patients with WBS are able to extract depth information from their visual environment, but that the use of this information to guide their movements seems to be impaired.

Methods

Experimental procedures

Subjects participated in four experiments. The first three experiments were aimed at the perception of depth using perspective, parallax and stereoscopic cues, respectively. The fourth experiment was aimed at the use of depth information to guide the movement of the hand. The procedures were approved by the medical ethical committee of the Erasmus MC, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

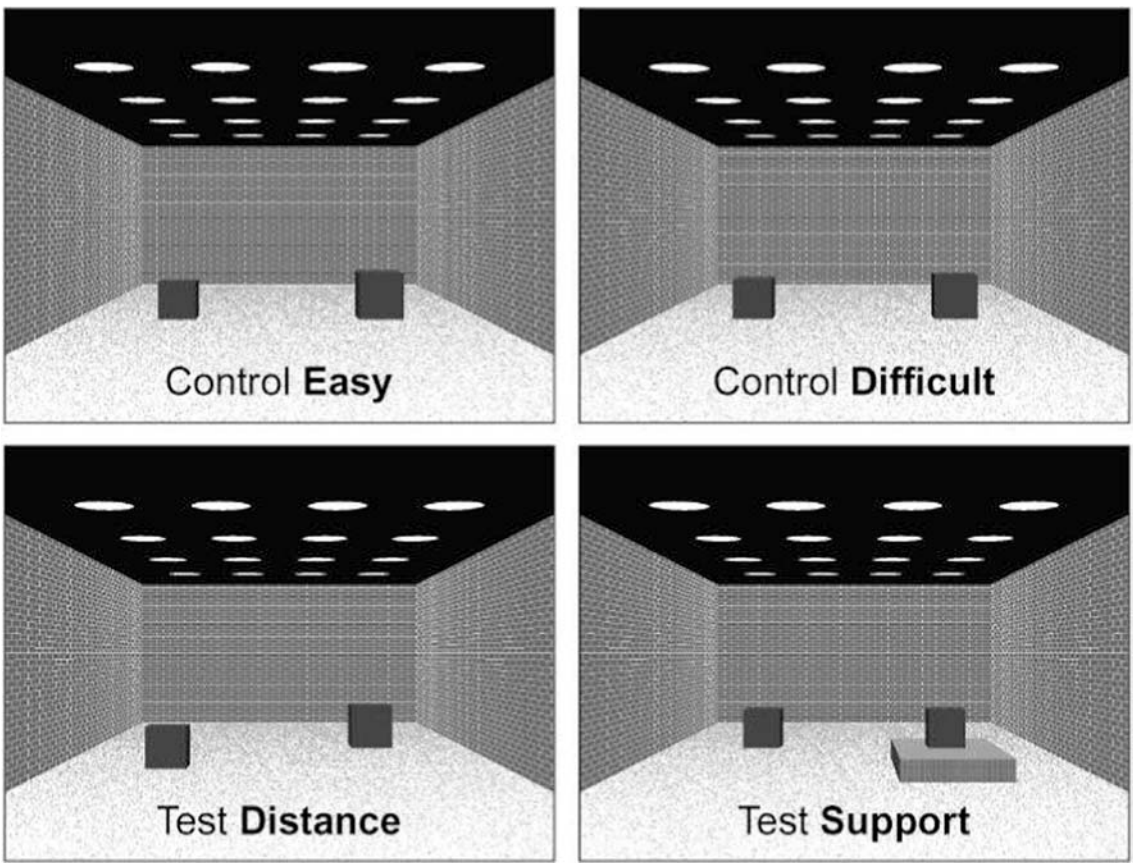


Fig. 1 The four conditions in the monocular depth experiment. See text for explanation

Perspective cues

The perception of perspective cues was tested indirectly by asking for judgments of size. If two objects have retinal images that are the same size, the object that is judged to be further away will be judged to be larger. The perceived distance to an object is determined by its spatial relationship with other objects. For instance, an object seems to be further away when it is higher in the field of view.

In each of the 60 trials of this paradigm, a colored image was presented on a 21-inch computer screen 70 cm in front of the subject. Each image contained two blue cubes placed on the left and the right side of a textured room that was rendered with appropriate perspective for the subject's viewpoint. In each trial, the subjects had to decide by forced-choice which one of the two blue cubes in the room was the largest. The order of the 60 trials and the side on which the "larger" cube was presented were both chosen randomly.

There were four different conditions (see Fig. 1). In the two control conditions, one of the two cubes was actually larger than the other (in pixels on the screen). The actual size difference could be large (18%; *control-easy*, 24 trials) or small (9%; *control-difficult*, 12 trials). These control conditions were included to verify that the subjects understood the requirements of the task.

In the two test conditions the two cubes had identical actual sizes (in pixels), but their sizes seemed different due to the configurations in the scene. Hence, if this influences the subjects' responses, we will have evidence that they are able to perceive the monocular depth cues. In the first test condition (*test-distance*, 12 trials), one of two identically-sized cubes was placed higher on the screen than the other cube, and therefore seemed to be further away and, hence, larger than the other one. In the second test condition (*test-support*, 12 trials), one of the cubes was placed on a gray block, and therefore seemed to be closer and, hence, smaller than the other one (Meng and Sedgewick 2001). The configurations in both test conditions were construed in such a manner that a full appreciation of the depth cues would yield an illusory size difference of 18% between the two blue cubes, as in the "easy" control condition.

Before the beginning of this paradigm, subjects were shown several pairs of blue paper squares and were asked to indicate the larger of the two. All subjects were able to do this practice task correctly, showing that they understood at least the nature of the task. Note that a consistent response in this task can only be given when a subject is sensitive to the depth cues provided. The statistical chance of having less than three errors when a subject is purely guessing is less than 0.002% in the control-easy condition (24 trials), and less than 2% in the other three conditions (12 trials).

Parallax: structure from motion

People can use motion cues alone to judge an object's shape, which requires the perceptual combination of moving elements (Ullman 1979). On a computer monitor, we presented two "circles" of dots with the same average velocity of dot motion. In one circle, all dots moved back-and-forth in the same direction, but the velocities were lower for dots nearer to the edges, as if they were placed on a rotating sphere. In the other circle, all dots moved back-and-forth at the same velocity (simulating a moving plane behind a disk-shaped aperture). There were 500 dots in each image. The two images were presented simultaneously on the left and right side of a computer screen. In each of the 20 trials presented, subjects had to report which image looked more like a rotating sphere. The chance of making more than 15 correct choices in 20 trials by guessing is less than 1%.

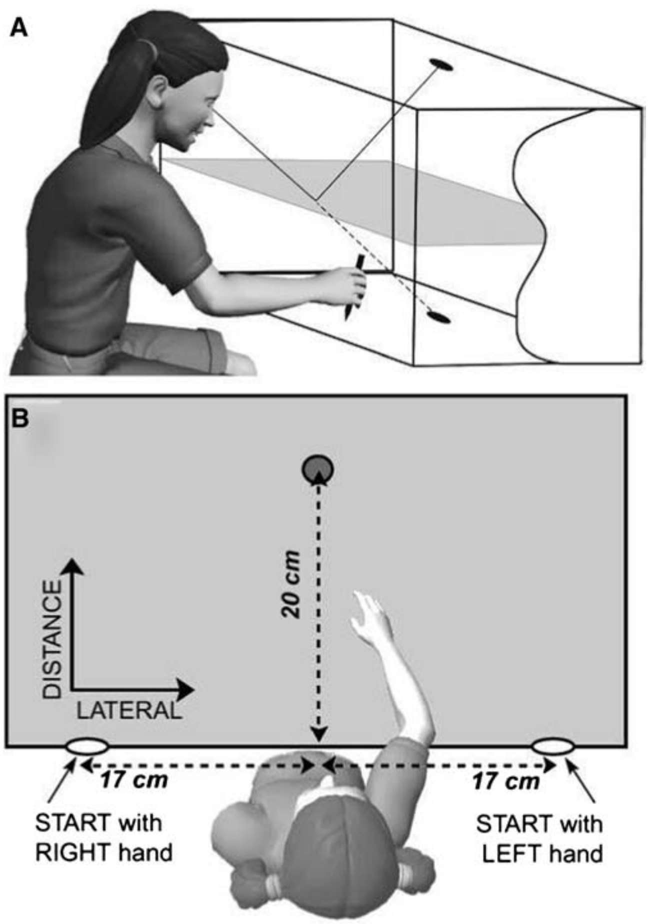


Fig. 2A–B Schematic drawings of the experimental set-up in the hand movement paradigm from the side (panel **A**) and from the top (panel **B**). Subjects were seated in the center, in front of the tablet, with the target about 20 cm directly in front. A movement was initiated from 17 cm left or right, depending on the handedness of the subject. Lateral and distance directions as used in the text are indicated

Stereopsis

The perception of stereoscopic cues was tested using the commonly used Titmus Stereo Test (Stereo Optical Co., Chicago, IL, USA). In this test, a patient is provided with properly-oriented Polaroid spectacles, so that each eye sees only one of two images that are polarized at 90° with respect to the other. This method induces a retinal disparity that can lead to a perception of depth at thresholds ranging between 3000″ and 40″ of arc at a viewing distance of 40 cm (see Von Noorden 1996, pp 275–276 for a description). The Titmus Stereo Test is especially suited for measuring stereopsis qualitatively in children. However, it should be noted that a failure to pass the test does not imply simply that the observer has no stereopsis, and therefore a failure should not be regarded as entirely conclusive (von Noorden 1996; Ohlsson et al. 2001). In the present study, performance was scored into one of four categories: *failed* when no stereoacuity could be measured; *good* when stereoacuity was better than 100″; *medium* when stereoacuity was between 400″ and 100″; or *coarse* when stereoacuity was above 400″. Performance scores were analyzed statistically using a chi-square test, with the significance level set at 0.05.

Movements

The use of depth information for guiding movements was tested using a task in which subjects had to point to a target with visual feedback (“closed-loop”) and without visual feedback (“open-loop”) about the position of their hand. The target was projected on a plane seen via a see-through mirror. The target was at a fixed position straight ahead of the subject. The subject had to move a pen with the dominant hand on a digitizing tablet (Ultrapad A2, WACOM Technologies Corporation, Vancouver, WA, USA) to the position at which the target was seen to lie on the tablet (see Fig. 2 for a pictorial description of the set-up).

Right-handed subjects (23 of the 30 WBS, 21 of the 22 CS, and three of the five MC subjects) started their pointing movements from the left (17 cm to the left and 20 cm below the target). Left-handed subjects (seven WBS, one CS, and two MC subjects) started their pointing movements from the right (17 cm to the right and 20 cm below the target). In this way the required movement of the whole arm was similar for left-handed and right-handed subjects.

The task consisted of two blocks each of ten trials. In the first block, the hand was visible through the mirror (*closed-loop condition*). In this condition, subjects could use both the visual information on the position of the target and the visual and proprioceptive information on the position of the hand to guide their hand to the target. In the second block, visual information about the position of the hand was removed by placing a sheet of paper beneath the mirror, so that only the target remained visible (*open-loop condition*). In this condition, subjects could use all the visual information on the target position, but only proprioceptive information on the hand to guide their invisible hand to the target. In other words, they had to integrate visual target information and proprioceptive hand information in order to point to the target.

The average and standard deviations of the lateral and distance positions (see Fig. 2) to which the subject pointed in each of the two conditions were calculated. The differences in the lateral and distance directions between the open-loop and closed-loop conditions were calculated individually. For the left-handed subjects, the sign of the lateral difference was reversed. A negative lateral difference is a setting that is in the direction of the starting position. A positive distance difference is a setting that is above the target position. Statistics on these differences were investigated using the Student’s *t*-test with the significance level set at 0.01.

Subjects

Informed consent to participate in this study was obtained from (the parents of) 33 patients with WBS (age range of 10–39 years; mean 18.9 ± 7.5 standard deviation). All patients showed the deletion of all genes (ELN, CYLN2, and so on) on the Williams Syndrome critical region on chromosome band 7q11.23 when tested genetically using fluorescent in situ hybridization (FISH) with four probes that cover the whole critical region. Furthermore, all patients showed the phenotypic characteristics of WBS. Based on parent and school reports, all WBS subjects were low functioning, with estimated total IQs below 80. All WBS subjects participated in a large number of behavioral experiments, including the experiments presented here. Thirty of the 33 subjects with WBS exhibited severe problems in descending stairs. For instance, they put two feet on each step, and made their movements slowly and carefully. All 33 subjects participated in the two experiments on perspective and stereoscopic cues. Seventeen subjects also participated in the structure-from-motion task, which was added later to the protocol. Thirty subjects (including the three subjects without difficulties in descending stairs) participated in the hand movement task.

Twenty-three control subjects (CS; age range of 6–30 years; mean 15.9 ± 9.0, matched as a group on chronological age) were recruited from the clinics and departments of the Erasmus MC. None of the CS had any problems in walking stairs. All subjects participated in the experiment on perspective cues; nine CS participated in the structure-from-motion task, and one CS did not participate in the hand movement task. Three control subjects who lack stereopsis were specifically recruited to participate in order to control for the absence of stereopsis on the hand movement task. They were excluded from the analysis of the stereopsis test.

A second group of atypical developing subjects of an unknown etiology but without WBS consisted of five subjects (MC: age range of 16–19 years; mean 17.7 ± 1.2) with a low level of cognitive functioning (mean total IQ: 75.8 ± 7.8). This group served as a grossly matched control group on age and IQ for the WBS group. None of these five MC subjects had problems in walking stairs, and all participated in the experiments described here.

Results

Depth perception

The results for the four conditions in the first monocular depth task (*perspective cues*) are presented in Fig. 3. Choices were considered to be "errors" if they were inconsistent with the monocular depth cue provided.

In the control conditions, one of the cubes was actually larger than the other. The statistical chance of having less than three errors when a subject is purely guessing is less than 0.002% in the control-easy condition (24 trials) and less than 2% in the control-difficult condition (12 trials). All 23 CS and all five MC subjects made fewer than three errors in these two control conditions, but five of the 33 WBS subjects made three errors or more in at least one of the control conditions. Therefore, we removed these five WBS subjects from further analysis of this task, since inability to respond correctly in the control condition confounds the results in the test conditions.

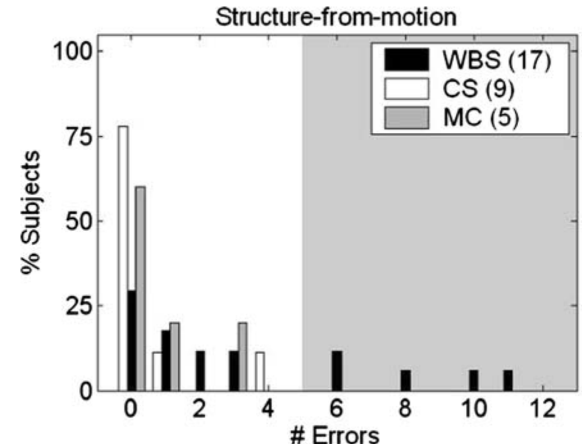
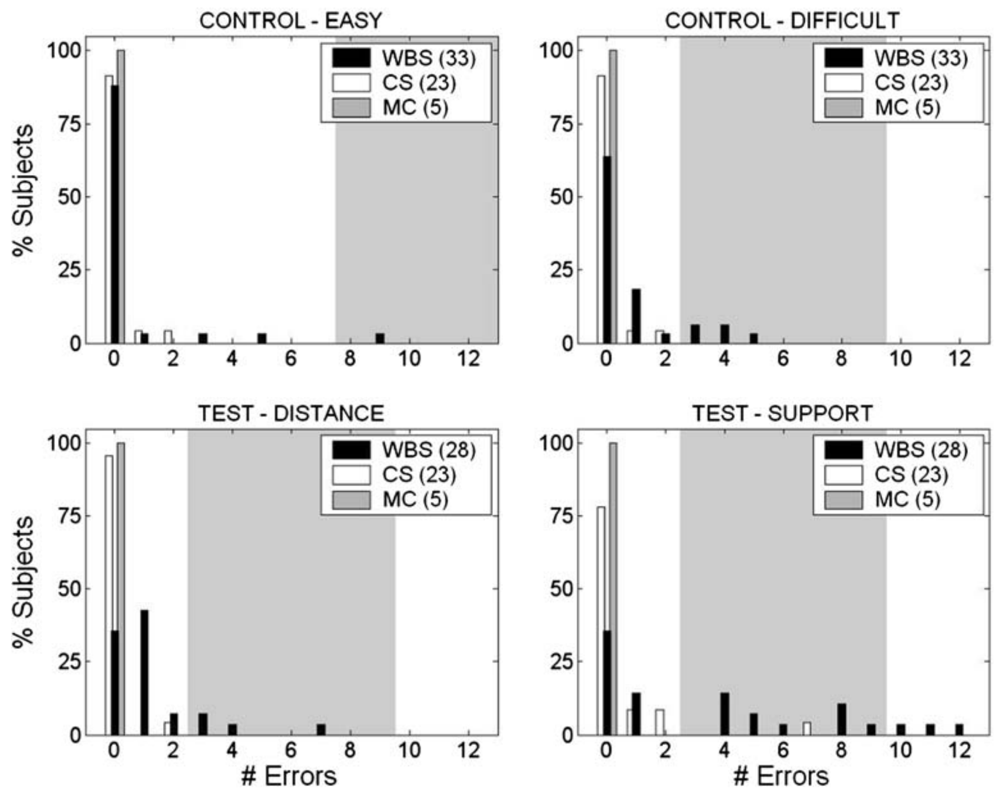


Fig. 4 The percentage of subjects making a given number of errors in the structure-from-motion task. The *light gray rectangles* indicate the range within the 95% confidence interval for a subject performing at chance

In the test conditions, the two cubes had identical sizes, but their sizes seemed different due to the configuration of the scene. The statistical chance of having less than three errors is less than 2% in these two conditions. In the test-distance conditions, all 23 CS, all five MC subjects and 24 of the 28 WBS patients included made fewer than three errors. In the test-support condition, 22 of the 23 CS, all five MC subjects and 14 of the 28 WBS patients included made fewer than three errors. Three of the 14 failing WBS patients systematically chose the

Fig. 3 The percentage of subjects that made a given number of errors in the four conditions of the monocular depth perception task. The *light gray rectangles* indicate the range within the 95% confidence interval for a subject performing at chance. This interval is different in the "control-easy" condition because more trials were presented in this condition (24 trials) than in the other three (12 trials). The five WBS subjects performing below chance in the two control conditions were removed from the analysis of the two test conditions. Note that three WBS subjects systematically indicated the wrong cube above chance in the test-support condition



"wrong" cube, perhaps indicating that they were considering the support as part of the object. The other 11 failing WBS subjects did not perform above chance. No correlation with age was observed ($R^2 = 0.03$).

In the structure-from-motion task, 12 of the 17 WBS subjects were able to indicate the simulated sphere on more than 15 of the 20 trials (see Fig. 4), indicating that these subjects could judge shape from the coherent motion of the dots. Seven of the nine tested CS and three of the five MC subjects made no errors at all, and the other four control subjects made fewer than five errors. Note that the chance of making less than five errors in 20 trials when a subject is guessing is less than 1%. No correlation was found with the scores on the other monocular depth task, nor with age ($R^2 = 0.08$).

Stereopsis

Table 1 shows the distribution of the scores in the stereopsis test in the WBS group and the control groups. One subject in the MC group failed to pass this test. Both groups contained subjects in all four nominal categories of stereoacuity. Group analysis showed that, although stereoacuity in WBS was lower than in control subjects ($X^2 = 25.3$), almost half of the patients with WBS showed fair stereovision (better than 400″). The three control subjects who were specifically selected for lacking stereopsis (and, indeed, did not pass the stereopsis test) were excluded from this analysis. In the WBS group, we did not observe any significant correlations with the results on both monocular depth tasks, nor with age ($R^2 = 0.01$).

Table 1 Stereopsis. The number of subjects (and percentages) in the group with Williams–Beuren Syndroom (*WBS*) and the control groups (CS and MC taken together) who failed the stereopsis test, or coarse (>400″), medium (100–400″) or good (<100″) stereoacuity

Group	*N*	Failed	Coarse	Medium	Good
WBS	33	16 (49%)	1 (3%)	13 (39%)	3 (9%)
CS + MC	25	3 (12%)	1 (4%)	3 (12%)	18 (72%)

The three control subjects who were selected to participate because they were known to lack stereopsis are not included in this table

Hand movements

Figure 5 shows examples of hand movement traces of two WBS patients and two control subjects in the control condition and in the test condition. All subjects could accurately move to the target position when their hand was visible (*closed-loop condition*), but they often made systematic errors when the hand was invisible (open-loop condition).

The differences in mean lateral and distance positions between the closed-loop condition and the open-loop condition for all subjects are plotted in Fig. 6. When analyzed individually, a significant overshoot (movement past the target in the distance direction) was observed in 16 of the 30 WBS patients participating in this

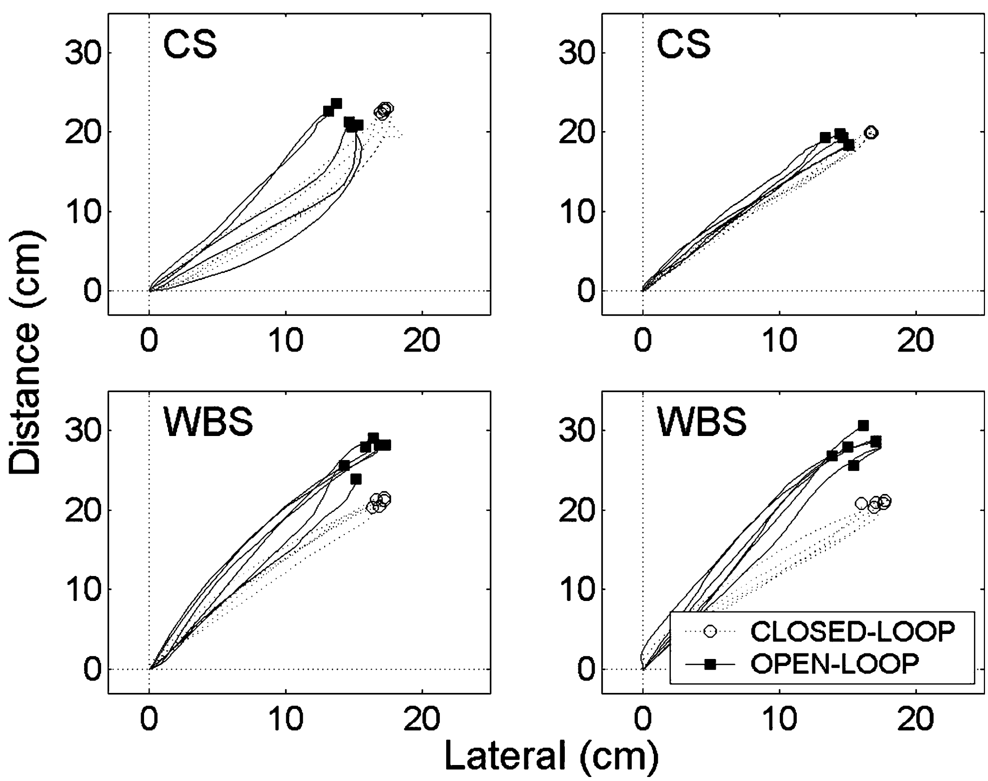


Fig. 5 Example of trajectories and the endpoints of hand movements toward the target with visual feedback (*dotted lines, open circles*) and without visual feedback (*solid lines, filled squares*). The *two top panels* show control subjects. The *two bottom panels* show patients with WBS. Note that the target coincided with the endpoints in the closed-loop condition

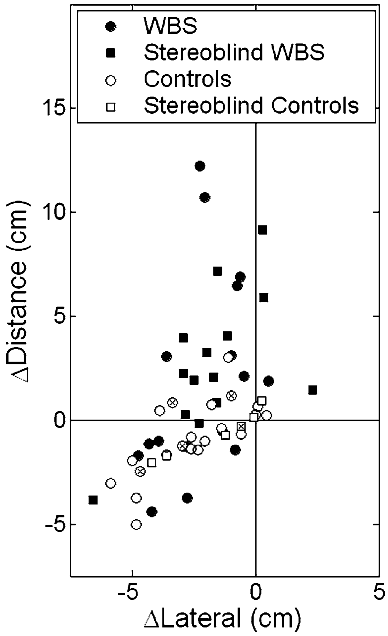


Fig. 6 The differences in pointing to the target between the settings in the closed-loop condition and the open-loop condition. For each subject, the average distance difference is plotted against the average lateral difference. For left-handed subjects, the sign of the lateral difference was reversed. *Filled symbols* represent WBS patients and *open symbols* represent control subjects (the combined CS and MC groups). *Squares* represent subjects without demonstrable stereopsis (stereoblind). The five control subjects of the MC group are marked with *crosses*

experiment (versus six of the 22 CS, and none of the five MC subjects). Furthermore, the radial differences between control and test condition (the absolute distance between target and pointing position) was significantly larger in the WBS group (4.7 ± 2.7 cm) than in the CS group (2.9 ± 2.1 cm) or the MC group (2.8 ± 1.8 cm).

Statistical group analyses across all 30 WBS subjects and 27 control subjects showed that, for the lateral direction, the WBS group did not differ significantly from two control groups (−2.0 ± 1.8 cm vs. −2.0 ± 2.2 cm for the CS group, $p = 0.57$; and vs. −0.9 ± 3.1 cm for the MC group, $p = 0.49$). Both the CS and the WBS group differed significantly from zero. This indicates that both WBS and the CS group showed a lateral difference in end-point position in the direction of the starting positions (for example, right-handed subjects moved their hand too far to the left).

For the distance direction, however, the WBS group (2.3 ± 4.2 cm) differed significantly from the CS group (−0.8 ± 1.7 cm) and the MC group (−0.4 ± 1.5 cm). On average the WBS group moved their hand too far with respect to the target position. The CS and MC groups did not differ significantly from zero ($p = 0.03$ and 0.60, respectively). No correlation with age was observed in any of the groups (all $R^2 < 0.2$).

As can be seen in Fig. 6 and Table 2, subjects without stereopsis did not differ from subjects with stereopsis, neither within the same group nor across the groups, and neither in the lateral nor the distance direction (all $p > 0.3$). Furthermore, we did not observe any correlation between the performance on the perspective and structure-from-motion tasks and the results from the hand movement paradigm (maximum R^2 obtained was 0.02, all $p > 0.5$).

Finally, Table 2 shows that the three WBS patients that did not have difficulties in walking stairs were comparable to the CS group. These three patients showed a negative lateral shift (in the direction of the starting point) and a tendency to undershoot the target in the distance direction. Their behavior contrasts to the overshooting behavior of some (but not all) of the other WBS patients who did have difficulties in walking stairs.

Discussion

In the present study, the perception of monocular and binocular depth cues and the use of visual depth information were tested in a group of patients with WBS. We

Table 2 Hand movements. The mean (and standard deviations) of the lateral and distance differences (in cm) in the hand movement task for the WBS group and the control group (CS + MC combined), and for the two groups when split in several subgroups based on their problems in walking stairs and their performance on the stereopsis task

Group	Stairs	Stereopsis	N	ΔLateral (cm)	$S_L < 0$ (%)	ΔDistance (cm)	$S_D > 0$ (%)
WBS			30	−2.0 (1.8)	57	2.3 (4.2)	53
	Problems		27	−1.9 (1.9)	52	2.6 (4.3)	59
		Failed	13	−1.7 (2.1)	54	3.0 (3.3)	69
		Low—good	14	−2.1 (1.7)	50	2.3 (5.2)	50
	Normal		3	−2.5 (1.3)	100	−0.6 (0.4)	0
		Failed	1	−2.3	100	−0.1	0
		Low—good	2	−2.6 (1.8)	100	−0.8 (0.3)	0
Controls	All normal		27	−2.0 (2.2)	57	−0.8 (1.7)	22
		Failed	6	−1.4 (2.1)	50	−0.6 (1.1)	17
		Low—good	21	−2.2 (2.2)	62	−0.8 (1.8)	24

N number of subjects in the group, $S_L < 0$ percentage of subjects showing a significant individual lateral shift in the direction of the starting point, $S_D > 0$ percentage of subjects showing a individual significant ($p < 0.01$) distance difference greater then the target position. Note that the number of controls who failed the stereopsis test now includes the three subjects who were especially recruited for their lack of stereopsis were inspired by their notable problems in descending stairs, which are often regarded as deficits in the perception of depth.

For the visual perception of depth, our results show that patients with WBS were able to judge size and shape from the (spatial) relationships between structures using perspective and parallax cues. Half of the patients with WBS did make more mistakes in the monocular depth perception task when depth was induced by a rather complex configuration of the elements in the room (the ‘‘test-support’’ condition). One might argue that the noted problems with global processing encountered by patients with WBS might hamper performance in such a complex situation, which represents one of the more extreme cues available in monocular depth perception. On the other hand, this result could also be attributed to more general deficits because the WBS group also made more errors in the other conditions of this task. We think that the poor performance of the five subjects who were excluded from the analysis of the monocular depth perception task is most likely due to a loss of interest, attention and/or concentration, since they did not differ obviously from the other patients in terms of the characteristics of WBS. Nonetheless, 24 subjects of the 28 included subjects showed a performance in this task that can only be reached when they can process monocular depth cues properly.

About 49% of our WBS patients were unable to perceive stereoscopic depth information properly, which is congruent with the incidence of 44% reported previously (Atkinson et al. 2001). Such a high incidence of reduced stereopsis in WBS is not surprising, since these patients show a much higher incidence of common visual problems in childhood, such as strabismus (Kapp et al. 1995) and reduced visual acuity (Atkinson et al. 2001), that are known to restrict the proper development of binocular processing of visual information.

With respect to the use of depth in guiding movements, we observed that patients with WBS could move accurately to a target in depth when they could see their hand (see Fig. 4), indicating that patients with WBS do not show motor problems in performing this task. However, their hand movements were impaired when they had no visual feedback about the position of their hand. On average they tended to move their hand too far with respect to the target position. Although the monocular depth perception task and the pointing experiment were not matched, it is striking to see that in the pointing experiment in which subjects could use all possible cues (and not only texture and perspective), the performance of WBS subjects was the worst.

We can conclude that the majority of patients with WBS are able to perceive and report depth, although the scores of the WBS group are on average lower than those of the control group. This suggests that their difficulties in visuo-motor activities, such as walking stairs, are not related to problems in the perception of visual depth. Rather, the use of visual depth information in guiding movements seems to be impaired when the movement is executed without continuous visual feedback (Atkinson et al. 1997, 2003). However, we cannot rule out the possibility that problems in proprioception in WBS play a role in the outcomes of the present study, although one might argue that such proprioceptive problems are also likely to show up in the control condition of the hand movement task.

Relevance of stereoblindness to motor control

As mentioned in the ‘‘Introduction’’, depth information can be extracted by both binocular and monocular cues in the visual environment. We did not observe any effect of the absence or presence of stereopsis on the accuracy of hand movements in either WBS or control subjects. Moreover, the five normal control subjects without stereopsis did not report any problems with walking stairs at all. Therefore, we conclude that the presence or absence of stereopsis is unlikely to have played an important role in the outcomes of our hand movement task. This is congruent with a previous report that stereo deficits were uncorrelated with performances on tests of spatial cognition (Atkinson et al. 2001). So, poor stereopsis cannot be the most prominent cause of the problems encountered when walking stairs in WBS. It seems likely that other factors, like motor problems, play a more significant role.

Relation to walking stairs

Problems in motor behavior have often been described in the diagnostic literature concerning WBS (MacDonald and Roy 1988; Trauner et al. 1989; Chapman et al. 1996; Withers 1996). Severe problems are commonly noted in walking on stairs in a majority of patients with WBS (for example, 30 of the 33 patients seen by our group). Also, the parents of patients often reported the problems in walking stairs when they were asked for any motor abnormalities of their child.

Their inability to descend steps smoothly is the most marked feature. They put two feet on the same step before continuing to the next step, they often use two hands to hold onto the banisters, and they tend to look down constantly to the steps ahead. Ascending stairs seems to pose fewer problems, although most of our subjects still climbed carefully. This observation might be related to the fact that a mis-step during climbing has less serious consequences than a mis-step during descending. Moving a foot too far during descending leads to overshooting the next step of the stairs, and yields the unacceptable risk of falling down. Such an overshooting foot movement would correspond to the overshoot observed in our hand movement task when the hand was not visible. During ascending, a mis-step is most likely to lead to a (harmless) touch of the next step with your foot.

Walking stairs adequately involves both the proper perception of visual depth and subsequently the proper use of the visual depth information in guiding one's movements. Normal subjects are quite able to descend stairs using one foot per step and walk without much direct visual feedback about the position of feet and stairs. In contrast, patients with WBS seem to prefer constant visual feedback about the relative positions of their feet and the steps ahead. Hence, they are likely to move more slowly and carefully. In this way they ensure that the stairs are walked safely without risk of getting hurt. This is consistent with our finding that WBS patients only perform their movements correctly when visual feedback is present, although we acknowledge that this analogy is somewhat speculative, as the depth cues provided in our experiments and those available in normal stair walking are quite different.

In our group, three patients with WBS did not show any problems in walking stairs, and, interestingly, their results in the hand movement task were similar to the control group. This suggests that, in contrast to the other patients, these three patients were able to use depth information to guide their movements adequately, although all patients shared the common genotype and clinical symptoms of WBS.

Limitations

In order to investigate depth processing in WBS, we employed four experimental procedures. This inevitably puts limitations on the ecological validity of the experiments. For instance, in real life, observers perceive and act on the basis of a real three-dimensional world with all depth cues provided simultaneously, instead of being forced to use each one separately. On the other hand, the procedures employed allowed for a quantitative and controlled comparison between subjects.

The procedures themselves might have introduced some limitations. In the monocular tasks, for instance, the sensitivity might be too low, since we were only asking for ordinal relationships (rather than metric depth). Therefore, it could be argued that monocular depth vision in WBS might be subnormal, but still above the threshold set in our task. Presenting a more elaborated task is likely to reduce these limitations, and may yield subtle deficits in WBS subjects. However, this has the serious drawback of inducing loss of interest, attention and concentration, which are common problems in WBS. These problems are probably the reason for the errors made by the WBS patients in the present experiments. This might be illustrated by the significant correlation between the total number of errors made in the two control conditions and the total number of errors made in the two test-conditions of the monocular depth perception task using the illusory room ($R^2 = 0.55$, $p < 0.001$).

Finally, we should remark that no detailed matching or scoring of IQ was done for the present experiments, so we cannot relate the present results with the alleged visuo-spatial deficits often observed in WBS. One has to realize that matching a control group to subjects is burdened with difficulty given the atypical cognitive profiles of those with WBS. Nonetheless, in our opinion, this possible shortcoming is unlikely to have had a significant effect on the outcomes of the experiments. For instance, age did not have a significant effect in any of the experiments (all $R^2 < 0.2$). Also, the group of low-functioning subjects without WS (the MC group) performed as well as the other subjects of the control group (the CS group). Furthermore, it should be noted that ten children were present too in that control group. We can remark that the perception tasks were designed such that a successful performance is proof of the appreciation of depth cues. The control conditions included in the tasks ensured that subjects understood the requirements of the task, and by comparing the results within subjects in the hand movement task, each subject served as his or her own control.

Neurophysiological basis

Although speculative, the observed problems in visuomotor coordination (hand movements and descending stairs) may be related to cortical deficits in the dorsal stream, since this occipitoparietal pathway is associated with the visuo-spatial processing and the visual control of action (Goodale and Milner 1992). Other studies have already implicated substantial problems with dorsal stream functioning in WBS [as well as in a number of other disorders (see, for example, Braddick et al. 2003)], whereas the ventral stream (occipitotemporal lobes), which is mainly involved in processing object properties, seems to be largely spared in WBS (Atkinson et al. 2001, 2003; Nakamura et al. 2002; Paul et al. 2002). Moreover, it has been suggested that WBS subjects seem to process visual information effectively but show problems when translating it into actions, which would be indicative of dorsal stream deficits (Atkinson et al. 1997).

Our observations may also reflect deficits in cerebellar functioning in WBS, since the cerebellum is strongly involved in motor activities. Structural MRI studies (Reiss et al. 2000; Schmitt et al. 2001) and neurological observations (Trauner et al. 1989; Bellugi et al. 1990; Chapman et al. 1996) do indeed suggest cerebellar disturbances in WBS, which have been recently related to the deletion of the gene CYLN2 in WBS (Hoogenraad et al. 2002). However, we did not observe signs of gross cerebellar deficits, such as the presence of ataxia, nystagmus or vestibular dysfunction in our patients, although the saccadic eye movements of subjects with WBS seems to suggest some cerebellar disturbances (Van der Geest et al. 2004).

Conclusion

We conclude that most patients with WBS are able to derive depth from spatial relationships between visual objects, despite their alleged problems in global visual information processing. Our results instead suggest impairment when using visual depth information to adequately guide movements, especially in conditions where visual feedback on the movement is lacking.

Acknowledgements The authors are grateful to the patients with Williams–Beuren Syndrome and their families for participating in this study. JN van der Geest was supported by grants from the NWO (903-68-394) and the Revolving Fund of the Erasmus MC. MA Frens was supported by a VIDI grant from the NWO.

References

Atkinson J, King J, Braddick O, Nokes L, Anker S, Braddick F (1997) A specific deficit of dorsal stream function in Williams' syndrome. Neuroreport 8:1919–1922

Atkinson J, Anker S, Braddick O, Nokes L, Mason A, Braddick F (2001) Visual and visuospatial development in young children with Williams syndrome. Dev Med Child Neurol 43:330–337

Atkinson J, Braddick O, Anker S, Curran W, Andrew R, Wattam-Bell J, Braddick F (2003) Neurobiological models of visuospatial cognition in children with Williams syndrome: measures of dorsal-stream and frontal function. Dev Neuropsychol 23:139–172

Bellugi U, Bihrle A, Jernigan T, Trauner D, Doherty S (1990) Neuropsychological, neurological, and neuroanatomical profile of Williams syndrome. Am J Med Genet Suppl 6:115–125

Bellugi U, Lichtenberger L, Mills D, Galaburda A, Korenberg JR (1999) Bridging cognition, the brain and molecular genetics: evidence from Williams syndrome. Trends Neurosci 22:197–207

Bellugi U, Lichtenberger L, Jones W, Lai Z, St George M (2000) The neurocognitive profile of Williams Syndrome: a complex pattern of strengths and weaknesses. J Cogn Neurosci 12:7–29

Bihrle AM, Bellugi U, Delis D, Marks S (1989) Seeing either the forest or the trees: dissociation in visuospatial processing. Brain Cogn 11:37–49

Braddick O, Atkinson J, Wattam-Bell J (2003) Normal and anomalous development of visual motion processing: motion coherence and "dorsal-stream vulnerability". Neuropsychologia 41:1769–1784

Chapman CA, du PA, Pober BR (1996) Neurologic findings in children and adults with Williams syndrome. J Child Neurol 11:63–65

Davies M, Udwin O, Howlin P (1998) Adults with Williams syndrome. Preliminary study of social, emotional and behavioural difficulties. Br J Psychiatry 172:273–276

Farran EK, Jarrold C, Gathercole SE (2001) Block design performance in the Williams syndrome phenotype: a problem with mental imagery? J Child Psychol Psychiatry 42:719–728

Francke U (1999) Williams–Beuren syndrome: genes and mechanisms. Hum Mol Genet 8:1947–1954

Van der Geest JN, Lagers-van Haselen GC, van Hagen JM, Govaerts LCP, de Coo IFM, de Zeeuw CI, Frens MA (2004) Saccade dysmetria in Williams-Beuren syndrome. Neuropsychologia 42:569–576

Goodale MA, Milner AD (1992) Separate visual pathways for perception and action. Trends Neurosci 15:20–25

Hoogenraad CC, Koekkoek B, Akhmanova A, Krugers H, Dortland B, Miedema M, van Alphen A, Kistler WM, Jaegle M, Koutsourakis M, Van Camp N, Verhoye M, van der Linden A, Kaverina I, Grosveld F, De Zeeuw CI, Galjart N (2002) Targeted mutation of Cyln2 in the Williams syndrome critical region links CLIP-115 haploinsufficiency to neurodevelopmental abnormalities in mice. Nat Genet 32:116–127

Kapp ME, Von Noorden GK, Jenkins R (1995) Strabismus in Williams syndrome. Am J Ophthalmol 119:355–360

Korenberg JR, Chen XN, Hirota H, Lai Z, Bellugi U, Burian D, Roe B, Matsuoka R (2000) Genome structure and cognitive map of Williams syndrome. J Cogn Neurosci 12:89–107

Kovacs I, Lukacs A, Feher A, Racsmany M, Pleh C (2001) Contour integration deficit in Williams Syndrome children [Abstract]. J Vis 1(3):146 (see http://journalofvision.org/1/3/146)

Lashkari A, Smith AK, Graham JM Jr (1999) Williams–Beuren syndrome: an update and review for the primary physician. Clin Pediatr 38:189–208

MacDonald GW, Roy DL (1988) Williams syndrome: a neuropsychological profile. J Clin Exp Neuropsychol 10:125–131

Meng JC, Sedgewick HA (2001) Distance perception mediated through nested contact relations among surfaces. Percept Psychophys 63:1–15

Mervis CB, Robinson BF, Bertrand J, Morris CA, Klein-Tasman BP, Armstrong SC (2000) The Williams syndrome cognitive profile. Brain Cogn 44:604–628

Morris CA, Mervis CB (2000) Williams syndrome and related disorders. Annu Rev Genomics Hum Genet 1:461–484

Nakamura M, Watanabe K, Matsumoto A, Yamanaka T, Kumagai T, Miyazaki S, Matsushima M, Mita K (2001) Williams syndrome and deficiency in visuospatial recognition. Dev Med Child Neurol 43:617–621

Nakamura M, Kaneoke Y, Watanabe K, Kakigi R (2002) Visual information process in Williams syndrome: intact motion detection accompanied by typical visuospatial dysfunctions. Eur J Neurosci 16:1810–1818

Von Noorden GK (1996) Binocular vision and ocular motility: theory and management of strabismus. Mosby, St Louis, MO

Ohlsson J, Villarreal G, Abrahamsson M, Cavazos H, Sjostrom A, Sjostrand J (2001) Screening merits of the Lang II, Frisby, Randot, Titmus, and TNO stereo tests. J Am Assoc Pediat Ophthalmol Strabismus 5:316–322

Olitsky SE, Sadler LS, Reynolds JD (1997) Subnormal binocular vision in the Williams syndrome. J Pediat Ophthalmol Strabismus 34:58–60

Osborne LR, Martindale D, Scherer SW, Shi XM, Huizenga J, Heng HHQ, Costa T, Pober B, Lew L, Brinkman J, Rommens J, Koop B, Tsui LC (1996) Identification of genes from a 500-kb region at 7q11.23 that is commonly deleted in Williams syndrome patients. Genomics 36:328–336

Paul BM, Stiles J, Passarotti A, Bavar N, Bellugi U (2002) Face and place processing in Williams syndrome: evidence for a dorsal-ventral dissociation. Neuroreport 13:1115–1119

Reiss AL, Eliez S, Schmitt JE, Straus E, Lai Z, Jones W, Bellugi U (2000) IV. Neuroanatomy of Williams syndrome: a high-resolution MRI study. J Cogn Neurosci 12:65–73

Sadler LS, Olitsky SE, Reynolds JD (1996) Reduced stereoacuity in Williams syndrome. Am J Med Genet 66:287–288

Schmitt JE, Eliez S, Warsofsky IS, Bellugi U, Reiss AL (2001) Enlarged cerebellar vermis in Williams syndrome. J Psychiat Res 35:225–229

Stiles J, Sabbadini L, Capirci O, Volterra V (2000) Drawing abilities in Williams syndrome: a case study. Dev Neuropsychol 18:213–235

Trauner DA, Bellugi U, Chase C (1989) Neurologic features of Williams and Down syndromes. Pediat Neurol 5:166–168

Udwin O, Yule W (1991) A cognitive and behavioural phenotype in Williams syndrome. J Clin Exp Neuropsychol 13:232–244

Ullman S (1979) The interpretation of structure from motion. Proc R Soc London B Biol Sci 203:405–426

Withers S (1996) A new clinical sign in Williams syndrome. Arch Dis Child 75:89