Impaired geometric reorientation caused by genetic defect

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The capacity to reorient in one's environment is a fundamental part of the spatial cognitive systems of both humans and nonhuman species. Abundant literature has shown that human adults and toddlers, rats, chicks, and fish accomplish reorientation through the construction and use of geometric representations of surrounding layouts, including the lengths of surfaces and their intersection. Does the development of this reorientation system rely on specific genes and their action in brain development? We tested reorientation in individuals who have Williams syndrome (WS), a genetic disorder that results in abnormalities of hippocampal and parietal areas of the brain known to be involved in reorientation. We found that in a rectangular chamber devoid of surface feature information, WS individuals do not use the geometry of the chamber to reorient, failing to find a hidden object. The failure among people with WS cannot be explained by more general deficits in visual-spatial working memory, as the same individuals performed at ceiling in a similar task in which they were not disoriented. We also found that performance among people with WS improves in a rectangular chamber with one blue wall, suggesting that some individuals with WS can use the blue wall feature to locate the hidden object. These results show that the geometric system used for reorientation in humans can be selectively damaged by specific genetic and neural abnormalities in humans.

geometric processing | neural specificity | Williams syndrome | navigation | spatial representations

When rats, human toddlers, or adults are disoriented in a chamber, they search for targets using geometric properties of the layout, often ignoring quite salient nongeometric cues (1–5). This pattern has led scientists to hypothesize that reorientation in animals (including humans) is guided by a cognitive module that engages geometric properties of layouts such as the lengths of surfaces, the angles of their intersections, and geometric sense (i.e., "left-" and "right-ness"), but does not engage nongeometric information such as surface color (2–4). Others have argued against the idea of a geometric module, proposing instead a model in which reorientation is guided by a range of information available in the environment, including both geometric and nongeometric properties. In the latter model, cues are selected and used on the basis of their reliability over the organism's learning history (6, 7). Both views, however, acknowledge that geometric representations of layouts are privileged, playing a primary role in reorientation across a large range of species.

This privileging of geometric representations in reorientation tasks resonates with the idea of domain specificity—one of the hallmarks of modular systems as proposed by Fodor (8). Other characteristic properties of modular systems include impenetrability, ontogenetic invariance, characteristic breakdown patterns and neural localization. Although much debate over the modularity of the geometric system that supports reorientation has focused on the criterion of impenetrability (2–4, 9), presence of these other properties would be informative with respect to this debate. Ontogenetic invariance is shown by the observation that chicks who have had no previous experience with rectangular spaces can nevertheless reorient using geometric properties of layouts, specifically the angles and distances of surfaces (10). Characteristic breakdown patterns are embodied in the typical error patterns observed among animals and humans (Fig. 1). Here, we advance our understanding of the reorientation system by showing selective and severe geometric impairment in individuals with Williams syndrome (WS), a neurodevelopmental disorder that results in a profile of selective but severe spatial impairment throughout life (11).

WS results from a microdeletion in chromosome 7q11.23 (12). People with WS have a profile of mild to moderate retardation and highly selective but severe impairment in a range of spatial tasks that normally engage parietal and other dorsal stream functions of the brain (13, 14). Recent imaging studies show structural and functional abnormalities of the occipital–parietal as well as hippocampal regions of the brains of people with WS (15–17)—regions known to be involved in navigation (18–23). Selective and severe impairment of the geometric representations used in reorientation among people with WS would provide evidence for neural localization, supporting the neural and functional specificity of the human reorientation system.

In experiment 1, 19 people with WS (mean age, 17 y; range 9 y, 9 months to 27 y 7 months) were tested in two conditions: a rectangular chamber with four black walls and an identical chamber except for a blue wall that replaced one of the shorter black walls (Fig. 1). In each condition, participants entered the chamber with the experimenter and watched as the experimenter hid a toy in one of the four corners. They then closed their eyes and were blindfolded for approximately 10 s as the experimenter disoriented them by turning them around in circles. Then they opened their eyes and searched for the hidden toy. If WS individuals show the hallmark pattern of responding that occurs among nonhuman species, human children, and adults, they should search the geometrically appropriate corners (corners C and R in Fig. 1) more often than the geometrically inappropriate corners (corners N and F in Fig. 1) in the all-black chamber.

Results

Fig. 2 presents the average proportion that individuals with WS searched each of the four corners (correct, rotationally equivalent, near, and far) collapsed over the four trials.* The data were first analyzed for each trial, examining how many participants searched the geometrically appropriate corners (C and R

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*In most developmental studies performance is analyzed using parametric statistics, such as *t* tests, based on proportions of search across the four corners (3, 5, 24, 25). In the current study, we use nonparametric statistics to avoid violating the assumptions of parametric tests. Note, however, that all of the data presented in this article were also analyzed using parametric statistics and the results remain the same.

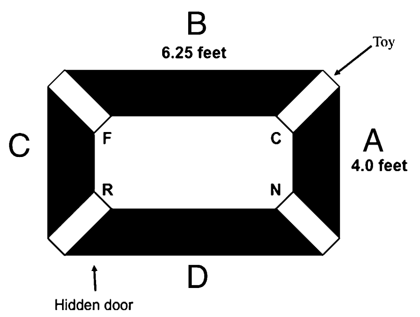

Fig. 1. Illustration of the testing environment for the current experiments. A, B, C, and D denote each of the four walls. In the black wall condition, all walls were black. In the blue wall condition, wall A was blue. C, R, N, and F illustrate the four corners in which the toy was hidden (with hiding location counterbalanced across participants). C, correct corner (i.e., corner where the toy was hidden); R, rotationally equivalent corner (i.e., the corner that is rotationally equivalent to the correct corner); N, near corner (i.e., the corner that is closest to the correct corner); F, far corner (i.e., the nonrotationally equivalent corner that is farthest from the correct corner). In previous studies using similar testing environments (see text), nonhuman species and human toddlers show characteristic breakdown patterns in their search for a hidden object, even when a feature, such as a colored wall, fully species the object's location. This characteristic breakdown pattern is to search at the correct corner (C) as well as the rotationally equivalent corner (R), suggesting that reorientation is based upon the geometry of the layout.

in Fig. 2) and the geometrically inappropriate corners (N and F in Fig. 2). The distribution of geometric versus nongeometric searches for trials 1 through 4, respectively, were as follows: 10 vs. 9, 7 vs. 12, 11 vs. 8, and 12 vs. 7. On all four trials, these data were not significantly different from chance (50%): χ^2 (1, n = 19) of 0.05, 1.32, 0.47, and 1.32 ($P > 0.05$) for trials 1 through 4, respectively. All of the analyses reported in this paper are two-tailed statistical tests unless otherwise noted. The data were then analyzed according to how many participants searched each corner (C, R, N, and F). On three of the four trials, these data did not significantly differ from chance (25%), χ^2 (3, n = 19) of 1.84, 3.11, and 3.11 ($P > 0.05$) for trials 1, 2, and 4, respectively. On trial 3, χ^2 (3, n = 19) of 8.16 ($P < 0.05$), the far corner was not searched by any of the participants.

The data were then collapsed over all four trials and we examined how many participants searched the geometrically appropriate corners (C and R) more often than the geometrically inappropriate corners (N and F). Five people showed this pattern, six showed the opposite pattern, and eight people searched the two corner types the same numbers of times (Wilcoxon signed-rank test, $z = -0.59$, $P = 0.55$). (See *SI Materials and Methods* for a replication of the results with 11 of the WS participants who were tested a second time at a later date).

The same experimental method yielded a qualitatively different pattern among 12 normal college-age participants, who searched at the geometric corners (C and R) on 97% of the trials. In addition, although people with WS often perform spatial tasks at the level of normally developing 3- to 4-y-old children (14), 3-y-old children in this task are known to search at the geometrically appropriate corners at levels greater than chance (24). We also found this pattern in a sample of fourteen 3-y-olds who were tested in our laboratory (*SI Materials and Methods*).

A very different pattern emerged for the chamber with one blue wall (Fig. 2). Examination of individual performance (n = 19) revealed the following distribution for geometric (corners C and R) versus nongeometric (corners N and F) search for trials 1 through 4, respectively: 15 versus 4, 15 versus 4, 15 versus 4, and 13 versus 6. On the first three trials, these data significantly differed from chance (50%): χ^2 (1, n = 19) of 6.37 (all $P < 0.05$). Furthermore, of the 15 people who searched geometrically, there was a tendency to search at the correct corner. On each of the first two trials, search at the correct corner was greater than search at the rotationally equivalent corner; these data significantly differed from chance (50%; correct vs. rotationally equivalent, for trials 1 and 2, respectively, 13 vs. 2, 12 vs. 3, χ^2 (1, n = 15) of 8.07, 5.40; $P < 0.05$). Search at the correct and rotationally equivalent corners for trials 3 and 4, respectively, did not significantly differ from chance (50%; 8 vs. 7, 7 vs. 6).

These results suggest impaired geometry for reorientation, with improved search in a geometric layout with one blue wall; specifically, the blue wall helped some participants find the target. Indeed, an analysis collapsing over all four trials, directly comparing the number of participants who searched the correct corner in the chamber with one blue wall more often than the correct corner in the chamber with four black walls revealed that 12 participants showed this pattern (corner C in blue > corner C in black), whereas only one participant showed the opposite pattern of search (Wilcoxon signed-rank test, $z = -3.01$; $P = 0.003$, i.e., six participants had the same number of correct searches in blue- and black-wall chambers). One possibility is that the blue wall was used as a simple beacon, attracting the attention of participants who then could use their body sense of left and right to choose between the two corners flanking the blue wall. However, this was not the case. The number of participants who chose the correct corner across the four trials was not significantly different for those who had the toy hidden near the blue wall (n = 9) compared with those who had the toy hidden far from the blue wall (n = 10): χ^2 (4, n = 19) of 3.78 ($P > 0.05$).

Moreover, although some have hypothesized that people may need to combine language with geometry for accurate search in the blue wall condition (3, 25), logistic regressions showed that neither participants' comprehension nor production of the terms

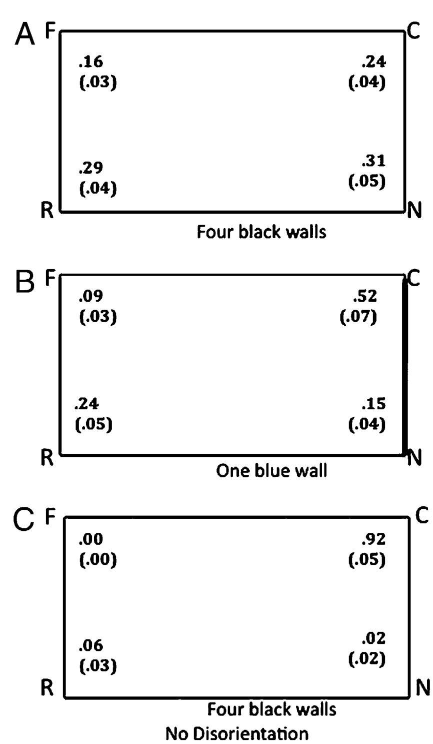

Fig. 2. Average proportion of search (and SEs) at each corner (correct, rotationally equivalent, near, and far) for the WS participants in experiment 1 (*A*, four black walls; *B*, one blue wall) and experiment 2 (*C*, four black walls, no disorientation)

"left/ right" reliably predicted search at the correct corner in the chamber with the blue wall (Table 1). Given that most individuals with WS who we tested showed no evidence of using geometric representations, it is perhaps not surprising that they could not use language in combination with geometry, as proposed by the language hypothesis (25). But our results also indicate that people with WS cannot successfully use language alone to encode the location of the hidden target.

The observed impairment in geometry among people with WS might have been a result of well documented deficits in visual–spatial working memory among people with WS (26–28), rather than being specific to reorientation. We tested this possibility in experiment 2, in which we used the all-black chamber to test people's memory for the location of the hidden toy in the absence of disorientation. Twelve people with WS (11 of whom had participated in experiment 1) watched as the experimenter hid the toy in one of the four corners. They were then blindfolded and were rotated to face one of the walls while the experimenter counted to 10. If participants' poor performance after disorientation were caused only, or principally, by the difficulty of maintaining a representation of the location of the toy over the 10-s delay, they should have had difficulty in this task as well. However, the WS participants performed nearly perfectly, searching for the toy in the correct corner 92% of the time (Fig. 2). Nine individuals performed at ceiling level (i.e., 100% correct).

We asked whether the observed geometric deficit in individuals with WS is related to IQ or to performance on a standardized visual–spatial construction task that is a strong diagnostic of the hallmark spatial deficit of people with WS (11). Results of logistic regressions (Table 2) showed that IQ significantly predicted geometric performance in both the black-wall and blue-wall conditions, but that the visual–spatial construction task [Differential Abilities Scale (DAS)] predicted geometric performance in only the black-walled room. The different relationship with the DAS suggests that different mechanisms might underlie performance in the two conditions, consistent with the evidence that different neurological substrates control geometric and feature-based responding in navigation tasks (19). The correlation with IQ might mean that retardation more generally affects the ability to construct and use geometric representations of layouts; additional studies with other populations such as Down syndrome would be relevant but have not been carried out to our knowledge. But given the quite uneven profile of spatial functioning in people with WS, including strengths in processing of biological motion (29), face perception (30), and object recognition (31), and given the characteristic spatial profile in individuals with WS who are not retarded (16, 17), it seems more likely that the relationship with IQ in the present study is a result of a third variable, perhaps the degree of damage to parietal and hippocampal areas. Imaging studies combined with behavioral data in people with WS could help resolve this issue.

Discussion

Our results show a clear pattern of severe impairment among people with WS in a classic reorientation task, with failures to construct and/or use a geometric representation of the layout. There was modest improvement when a single blue wall was present, but given the failure in the all-black chamber, it is unlikely that participants were integrating a representation of the unique wall with a geometric representation of the layout. Rather, in the blue-walled chamber, participants may have been relying on an alternative mechanism, possibly using view-dependent representations to identify the correct corner (32).

Growing evidence suggests that the neural foundation of the representations that support reorientation is in the hippocampus and surrounding areas. Hippocampal place cells of the rat are sensitive to the overall geometry of layouts (22), and this sensitivity develops with exposure to a particular geometry and persists over time (33). Evidence from chicks suggests that the right hippocampus may be specialized for representing geometric information (34). Hippocampal lesions in pigeons likewise result in impairments in using geometric, but not featural, information to locate food in a rectangular arena (35). Hippocampal-lesioned rats can locate a submerged platform using a single black wall as a "polarizing" cue, even though they cannot use the geometric layout of the environment to do so (19). These patterns of performance resonate with the enhanced ability of our WS participants to use the blue wall to locate the hidden toy, even though they could not use the geometry of the layout to do so.

The neural evidence on reorientation among humans is more fragmentary, but still points to the likely role of the hippocampus. Hippocampal damage is associated with topographical disorientation, often in combination with damage to the parietal areas, consistent with the idea that there are strong interactions between these areas (18). The hippocampal impairment in people with WS, however, does not appear to be caused solely by abnormal input from the parietal areas, which are known to be impaired in WS (16). Imaging studies showed that neither faces

Table 1. Logistic regression analysis for left/right comprehension and production predicting correct performance in the blue wall chamber of experiment 1

Predictors	Blue wall: correct corner *B*	SE *B*	e^B	R^2
Left/right comprehension	−1.108	0.920	0.330	0.032
Left/right production	−0.501	0.858	0.606	0.007

e^B, exponentiated *B*.

Table 2. Logistic regression analysis for measures of IQ and block construction predicting geometric response (in the black chamber) and correct performance (in the blue wall chamber) in experiment 1

Predictor	Four black walls: geometric corners (C and R)				Blue wall: correct corner			
	B	SE *B*	e^B	R^2	*B*	SE *B*	e^B	R^2
Overall IQ	0.060	0.024	1.061*	0.158	0.053	0.022	1.054*	0.113
DAS pattern construction	0.039	0.015	1.040*	0.123	0.009	0.014	1.009	0.007

Scores for reorientation performance are taken from search at the geometric corners (correct plus rotationally equivalent corner) in the chamber with all black walls and search at the correct corner only in the chamber with one blue wall. Standardized measures include IQ from the Kaufman Brief Intelligence Test (37), and age equivalence for the Pattern Construction test from the DAS (38). Left/right comprehension and production data were collected for 16 participants. In the production task, a 3-cm x 3-cm square was displayed in the middle of a computer screen with a smiley face placed next to one of its sides (left, right, top, bottom). On each trial, participants were asked, "Where is the smiley face to the square?" They answered by labeling the position of the smiley face (e.g., left, right). In the Comprehension task, participants were given a 20-cm × 14-cm paper with a 3-cm × 3-cm square drawn at the center. They were asked to point to "the left [or right/top/bottom] side of the square." In each task, each term was tested four times, for a total of 16 trials [task was taken from Dessalegn and Landau (39)]. In the Production task, participants correctly identified the location of the smiley face for terms left/right on 72.75% (SD, 30.35%) of the trials, whereas in the Comprehension task they correctly pointed to the left/right side on 71.62% (SD, 25.89%) of the trials. In both tasks participants scored above 90% for the terms "top" and "bottom" (M production, 99.52; SD, 0.02; M comprehension, 92.05; SD, 0.22). e^B, exponentiated B.

*Significant at $P < 0.05$.

nor houses—stimuli linked to more ventral versus dorsal areas of the brain—activated the hippocampal formation in people with WS who have IQs within the normal range (17). Deficits in activation level during functional imaging, reduced resting blood flow, and abnormally low syntactic activity, especially in the anterior hippocampus, suggest functional impairment of neurons in this area (17). This possibility is consistent with research showing structural abnormalities of the hippocampal neurons in genetically altered mice modeled on WS; these mice also show abnormalities in navigation (36). Continuing studies of navigation in mouse knockout models along with studies of navigation in humans with WS is likely to lead to exciting new insights into the links among genes, brain development, and spatial representation.

In sum, our findings are consistent with neural specificity of the geometric system involved in reorientation in humans, adding to our understanding of the nature of this system and its continuity with other species. Whether this system is modular or depends on the use of multiple interacting cues, our studies show that damage to human parietal and hippocampal areas stemming from a genetic deficit can result in loss of the ability to construct and/or use geometric representations of spatial layouts. This neural specificity will naturally play an important role in further construction of theories explaining the remarkable capacity of humans and other species to reorient in space.

Materials and Methods

Participants were individuals with WS, a genetic disorder that presents with a profile of characteristic physical and neurological abnormalities including structural and functional abnormalities of the occipital–parietal and hippocampal regions of the brain (15–17). Typically, people with WS also have cognitive abnormalities, including mild to moderate mental retardation, highly selective and severe impairment in a range of visual–spatial tasks, and very strong language capacities (11). Our sample of people with WS fit this cognitive profile (as detailed later). All WS participants have the characteristic genetic deletion on the long arm of chromosome 7, as determined by FISH.

Experiment 1: Disorientation (All-Black Chamber and Blue-Walled Chamber). Participants were 19 individuals with WS (10 females; mean age, 16 y, 10 months; range, 9 y, 9 months to 27 y, 7 months), who were recruited through the WS Association and tested in the language and cognition laboratory of one of the authors (B.L.).

To assess the cognitive profile of the WS participants, two standardized tests were administered: the Kaufman Brief Intelligence Test (37) and the Pattern Construction test of the DAS (38). The Kaufman Brief Intelligence Test yields an overall IQ score and the Pattern Construction test of the DAS requires participants to copy the overall pattern of a model by assembling sets of blocks. Participants had an average IQ of 67.05 (SD, 12.35; range, 40–88). Their average performance on the Pattern Construction test was at the 1.58 percentile for their chronological age, reflecting the typical spatial deficit that has been observed for individuals with WS (11).

Methods were patterned after those of Hermer and Spelke (3, 4). Experiments 1 and 2 were conducted in an enclosed $6.25 \times 4.0 \times 9.58$–ft rectangular chamber. The four walls were covered with black felt in experiment 1 and one of the short walls (4.0 ft) was covered with blue felt in experiment 2. The chamber was illuminated by four lights mounted in the center of each of the four walls. A door was positioned along one of the longer walls, and after the participant and experimenter entered the chamber, the black felt was stretched across the door to conceal it. Four identical panels of red felt (9.58 ft high) hung from each of the four corners and served as hiding locations for a small toy bunny. A white noise generator ensured that participants could not use extraneous sounds as beacons.

Before entering the reorientation chamber, participants were told that they would help the experimenter find a hidden toy and were shown how the "disorientation" would occur. The participant closed his/ her eyes, and the experimenter and participant locked arms; the experimenter then slowly rotated with the participant in one direction; after several rotations the arms were switched and the pair rotated in the opposite direction. After practicing this procedure, the participant and experimenter entered the reorientation chamber. As the participant watched, the experimenter hid the toy behind a red felt panel in a predetermined corner and then pointed to its hiding location to ensure that the participant knew where the toy had been hidden. The experimenter then covered the participant's eyes with a blindfold. In experiment 1, the experimenter then linked arms with the participant and slowly rotated with him/her for 10 s, switching the direction of the rotation two to four times. When the participant was disoriented (as confirmed by his or her inability to correctly point to the location of the hidden door), the experimenter then turned the participant toward a wall and removed the blindfold. Each of the four walls was used once for each participant, and the order in which people faced each of the walls was randomly determined before the experiment. When the participant faced the wall, the experimenter stood directly behind the participant, looking down at the floor to avoid cueing the participant about the toy's location. Participants were asked to open their eyes and search for the hidden toy. Responses were coded online by the experimenter.

In keeping with the procedure used in many reorientation studies (3, 24), the hiding location of the toy remained constant across the four test trials for all experiments. Hiding location for each participant was selected before the experiment and was counterbalanced across participants. In experiment 1, half the participants were tested in the all-black condition before the blue-wall condition and half in the reverse order.

Experiment 2: No Disorientation. Participants were 12 individuals with WS (eight females; mean age, 18 y, 10 months; range, 11 y, 2 months to 29 y, 3 months). Eleven of the 12 participants also participated in experiment 1 (tested an average of 25.64 months after having participated in experiment 1; range, 0–39 months). Seven of the 12 participants participated in the replication of experiment 1 (*SI Materials and Methods*), and five of the 12 participated in the two experiments on the same day. Using the same instruments as in experiment 1, participants had an overall average IQ of 67.17 (SD. 11.38; range, 48–88). Their average performance on the Pattern Construction test was at the 1.17 percentile for their chronological age.

The method was identical to that of experiment 2, except that participants were not disoriented. Rather, after hiding the toy, the experimenter blindfolded the participant and then turned him/her to a predetermined wall, where the experimenter counted to 10. Then, the blindfold was removed and the participant was asked to find the toy.

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