PAPER

Developmental trajectories for spatial frames of reference in Williams syndrome

Marko Nardini,[1] Janette Atkinson,[2] Oliver Braddick[1] and Neil Burgess[3]

1. Department of Experimental Psychology, University of Oxford, UK
2. Department of Psychology, University College London UK
3. Institute of Cognitive Neuroscience and Department of Anatomy, University College London, UK

Abstract

Williams syndrome (WS) is a genetic disorder associated with severe visuocognitive impairment. Individuals with WS also report difficulties with everyday wayfinding. To study the development of body-, environment-, and object-based spatial frames of reference in WS, we tested 45 children and adults with WS on a search task in which the participant and a spatial array are moved with respect to each other. Although individuals with WS showed a marked delay, like young controls they demonstrated independent, additive use of body- and environment-based frames of reference. Crucially, object-based (intrinsic) representations based on local landmarks within the array were only marginally used even by adults with WS, whereas in typical development these emerge at 5 years. Deficits in landmark use are consistent with wayfinding difficulties in WS, and may also contribute to problems with basic localization, since in typical development landmark-based representations supplement those based on the body and on self-motion. Difficulties with inhibition or mental rotation may be further components in the impaired ability to use the correct reference frame in WS.

Introduction

Williams syndrome (WS) is a genetic disorder caused by a microdeletion on chromosome 7 (q11.23) (Ewart, Morris, Atkinson, Jin, Sternes, Spallone, Stock, Leppert & Keating, 1993) with estimated prevalence between 1 in 7500 and 1 in 25,000 (Stromme, Bjornstad & Ramstad, 2002; Greenberg, 1990). WS is associated with severe learning difficulties; however, individuals with WS typically show an uneven cognitive profile, with marked visuospatial impairments that contrast with relatively fluent language and high sociability (Bellugi, Bihrle, Jernigan, Trauner & Doherty, 1990; Atkinson, Anker, Braddick, Nokes & Mason, 2001). Within the visuospatial domain, impairments in WS are most pronounced in drawing and construction tasks, while object and face recognition are less impaired (Wang, Doherty, Rourke & Bellugi, 1995). These dissociations are of great interest for understanding the organization of different cognitive functions and the genetic mechanisms for their typical development in the brain (Meyer-Lindenberg, Mervis & Berman, 2006).

Spatial localization in Williams syndrome

Profound difficulties with visuospatial construction, including block design copying and drawing (Bellugi *et al.*, 1990), are a hallmark of WS. These difficulties are not accounted for by primary sensory problems (Atkinson

et al., 2001), and children and adults with WS also have difficulties on perceptual and spatial tasks without significant motor demands, including remembering locations on a screen (Paul, Stiles, Passarotti, Bavar & Bellugi, 2002; Vicari, Bellucci & Carlesimo, 2005, 2006), keeping track of moving objects (O'Hearn, Landau & Hoffman, 2005), and judging spatial relations between stimuli presented simultaneously (Landau & Hoffman, 2005; Farran & Jarrold, 2005). These findings indicate that the WS cognitive profile includes impairments in the ability to represent spatial information.

Convenience of testing has dictated that most spatial localization tasks used with WS have involved simple localization by a stationary participant within a stationary environment (e.g. Paul *et al.*, 2002; Vicari *et al.*, 2005, 2006). Such tasks can usually be solved with the use of any of the available body-, environment- or object-based reference frames alone or in combination: without a manipulation involving relative movement of the body, objects or environmental cues the use of these frames of reference cannot be dissociated (see e.g. Burgess, Spiers & Paleologou, 2004). So, although deficits in simple localization tasks are often interpreted in terms of impaired egocentric representations dependent on the dorsal stream (see below), it is also possible that such deficits arise from impaired use of environment- or object-centred representations. Here we use our spatial array paradigm (developed in Nardini, Burgess, Breckenridge & Atkinson,

Address for correspondence: Marko Nardini, Department of Experimental Psychology, Oxford University, South Parks Road, Oxford OX1 3UD, UK; e-mail: marko.nardini@psy.ox.ac.uk

2006) to determine whether the spatial deficit in WS can be identified with a specific reference frame or frames.

Impairments in the use of environment- or object-based reference frames would predict difficulties with everyday navigation and landmark use. The literature here is not so clear, as there have been few studies of navigation in WS. However, there are hints that it should be investigated, since families report that individuals with WS do have difficulties finding their way around; for example, on a questionnaire for parents of children with WS, one-third reported that their child had difficulties with wayfinding (Atkinson *et al.*, 2001). In addition, two adults with WS showed a marked impairment in searching for objects in a room-sized space (Smith, Gilchrist, Hood & Karmiloff-Smith, 2006), and individuals with WS have shown deficits in large-scale route learning (Farran, Tranter, Blades & Boucher, 2007) and on a standard spatial reorientation task (Lakusta, Dessalegn & Landau, 2006). Recent imaging studies (see below) also show that neural substrates for both body- and landmark-based spatial memory are atypical in WS.

Neural bases of visuospatial impairments in Williams syndrome

It has been hypothesized (Atkinson, King, Braddick, Nokes, Anker & Braddick, 1997; Atkinson, Braddick, Anker, Curran, Andrew, Wattam-Bell & Braddick, 2003) that one basis for the WS visuospatial impairment is in impaired processing in the dorsal visual stream, projecting to parietal lobe, which is specialized for object localization (Ungerleider & Mishkin, 1982) and the visual control of action (Milner & Goodale, 1995). The ventral visual stream, projecting to temporal lobe and specialized for face and object recognition, is less impaired. Consistent with this, individuals with WS show relatively good performance on visual recognition for faces (Wang & Bellugi, 1994; Paul *et al.*, 2002; Tager-Flusberg, Plesa-Skwerer, Faja & Joseph, 2003) and objects (Vicari *et al.*, 2005; Landau, Hoffman & Kurz, 2006), associated with the ventral stream (although their face processing is not necessarily typical; Donnai & Karmiloff-Smith, 2000). They are, however, severely impaired on dorsal-stream functions such as discriminating coherent motion (Atkinson *et al.*, 2003; Atkinson, Braddick, Rose, Searcy, Wattam-Bell & Bellugi, 2006; see also Reiss, Hoffman & Landau, 2005), action planning in a visuomotor 'post-box' task (Atkinson *et al.*, 1997; Dilks, Hoffman & Landau, in press) and visuomotor ability assessed on the Movement Assessment Battery for Children (Henderson & Sugden, 1992; Atkinson, Braddick, Anker, Ehrlich, Macpherson & Rae, 1996). Children with WS are additionally impaired on 'frontal' tests of executive function, particularly those that require a spatially directed response (Atkinson *et al.*, 2003).

Neuroimaging has recently provided evidence that dorsal stream (parietal lobe) abnormality is indeed implicated in the WS spatial deficit. Grey matter reductions are found in superior parietal lobe with structural MRI (Eckert, Hu, Eliez, Bellugi, Galaburda, Korenberg, Mills & Reiss, 2005), and in regions including the intraparietal sulcus (Meyer-Lindenberg, Kohn, Mervis, Kippenhan, Olsen, Morris & Berman, 2004; Reiss, Eckert, Rose, Karchemskiy, Kesler, Chang, Reynolds, Kwon & Galaburda, 2004) using voxel-based morphology. Depth of intra-parietal sulcus is also reduced in WS (Kippenhan, Olsen, Mervis, Morris, Kohn, Lindenberg & Berman, 2005). Functional imaging comparing shape matching and square completion (analogous to block construction) tasks found intact ventral stream activation, but abnormal dorsal stream activation in WS (Meyer-Lindenberg *et al.*, 2004).

The hippocampal formation in WS has also recently been found abnormal in structure and function (Meyer-Lindenberg, Mervis, Sarpal, Koch, Steele, Kohn, Marenco, Morris, Das, Kippenhan, Mattay, Weinberger & Berman, 2005), which is relevant to the use of external frames of reference (including landmarks) in WS, since the human hippocampus has a crucial role in navigation and landmark use (Burgess, Maguire & O'Keefe, 2002). Using PET and functional MRI, Meyer-Lindenberg and colleagues found profound reduction in resting blood flow, and no hippocampal activation above baseline for visual face and house stimuli, which show increased activation in controls. MRI and spectroscopic measures also indicated structural changes and reduced synaptic activity.

The spatial array paradigm

To measure the ability of children and adults with WS to remember locations using different spatial frames of reference, we used a task with which we have previously studied typically developing 3–6-year-olds (Nardini *et al.*, 2006). This enabled us to compare developmental trajectories for spatial frames of reference in WS with those previously measured in typical development. In this task, adapted from an adult change detection paradigm (Wang & Simons, 1999), participants see an object hidden under one of an array of cups placed on a movable board on the floor. Distinctive toys, which can potentially serve as landmarks, are fixed along two edges of the board. After seeing the object hidden, the participant and/or the board are moved. The participant is then asked to point to where the object was hidden.

Rotation of either the participant's viewpoint, or of the array of cups and local landmarks (or rotation of both or neither) between presentation and test determines which of the array-, body- or environment-based frames of reference will be available to support performance (see Figure 1). In all cases, the object's location does not change relative to the array, so an array-based frame of reference (FoR) can always support performance. When the array alone is rotated between presentation and test, only the array-based FoR can support performance. When the participant walks around the array, the environment-based FoR can also support performance
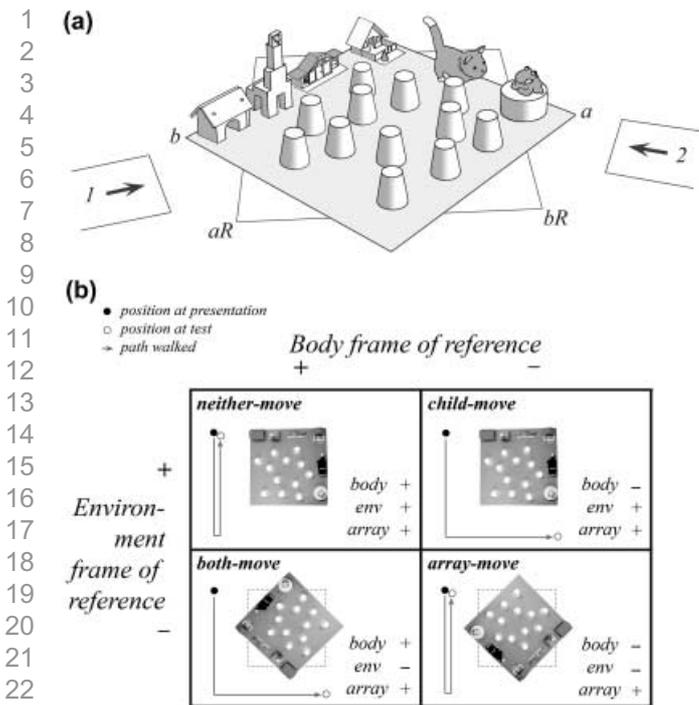
Figure 1 *The apparatus (a). Before search, the hidden object's place in terms of the* body frame of reference *(i.e. the angle from which participants viewed the array) could be changed either by walking the participant to a new position (*participant-move *condition; e.g. walk from* 1 *to* 2*), or by rotating the board (*array-move *condition; e.g. board rotates* a *to* aR *while participant walks from* 1 *halfway to* 2*, and back to* 1*). When participant position changed and the board rotated (*both-move *condition), the original viewing angle was matched, and therefore the* body FoR *correctly indicated the object's location (e.g. participant walks* 1 *to* 2 *while board rotates* b *to* bR*; see also circles indicating participants' positions at presentation and test in the lower diagram). In the baseline* neither-move *condition, the participant walked halfway to the other position and back and the board was not rotated. These four conditions (b) systematically varied the hiding place's consistency with* body-based *and* environment-based *frames of reference. The frame of reference provided by the* array *itself was always consistent between presentation and test. This frame of reference provided the only basis for correct retrieval in the* array-move *condition. Figure adapted from Nardini* et al. *(2006).*

(because the object's location does not change relative to the environment), but the body-based FoR cannot. Conversely, when the participant walks around the array and the array also rotates by the same amount, the body-based FoR can be used (because the object's location relative to the participant's body does not change), but the environment-based FoR cannot be used. Finally, when both participant and array stay in the same place, any of the above frames of reference can support performance.

Overall, the four conditions embody a 2 × 2 design in terms of consistency or inconsistency of the test array with body-based and environment-based FoRs (see Figure 1b). The different conditions are described in detail

in the Method section. We initially describe the design in terms of available frames of reference (to which our manipulations directly correspond), and not in terms of underlying representations which may enable their use. For example, use of an 'environment-based' FoR implies that participants' coding of location depends on the target's place in the framework of the surrounding space, but this coding might depend on either spatial updating or use of landmarks in the room. The types of representations, processes and neural systems which might support the use of the various frames of reference are considered in the Discussion.

In typical 3–6-year-olds, developmental trajectories for different spatial frames of reference were dissociated on this task (Nardini *et al.*, 2006). Children in all age groups showed an ability to use environment-based FoRs – indicated by increased accuracy in the conditions in which the array did not rotate relative to the room. In addition, they showed a weaker but consistent ability to use body-based FoRs – indicated by slightly better accuracy when participant and array maintained their positions relative to each other (i.e. both stayed still or both rotated together). The ability to use either FoR individually appears to contribute additively to performance when both FoRs can be used. Ability to recall locations solely using the array-based FoR – tested when the array is rotated alone – emerged at 5 years and increased with age. Again, ability to use the array-based FoR appears to contribute additively to performance in the other conditions.

In the present study we evaluated, using this same task, (1) whether individuals with WS show ability to use both body-based and environment-based frames of reference, (2) whether individuals with WS show ability to use an array-based frame of reference, and (3) how these abilities develop and change across the lifespan in WS. To account for the considerable variability in cognitive outcome in WS, we also analysed scores in terms of participants' verbal age.

Method

Participants

We tested 45 participants with WS with ages ranging from 5 to 42 years, recruited through the Williams Syndrome Foundation, UK. Participants had been diagnosed by medical professionals based on phenotypic and medical characteristics including heart defects and hypercalcaemia; for 23, the results of a fluorescence in situ hybridization (FISH) test were available to us. A deletion of the elastin gene on chromosome 7 (q11.23) was confirmed in all these individuals. For analysis the sample was divided into five age groups: 5–7 years, 8–11, 12–15, 16–23, and 26–42. Table 1 details characteristics of these groups, including verbal ages measured on the British Picture Vocabulary Scale (short form) (BPVS; Dunn, 1997). Participants, or parents of participants,

Table 1 *Characteristics of WS groups in the study and comparison control groups from Nardini* et al., *2006*

Group	N	Male : Female	Mean chronological age, years (SD)	Mean verbal age, years (SD)
WS 5–7	6	4 : 2	6.5 (1.1)	5.6 (1.2)
WS 8–11	8	6 : 2	10.3 (1.1)	7.0 (1.4)
WS 12–15	7	4 : 3	14.0 (1.3)	7.7 (3.1)
WS 16–23	12	4 : 8	20.1 (2.7)	9.6 (2.6)
WS 26–42	12	5 : 7	32.6 (5.1)	11.1 (3.6)
Control 3	18	9 : 9	3.5 (0.3)	–
Control 4	21	11 : 10	4.5 (0.3)	–
Control 5	17	8 : 9	5.5 (0.3)	–
Control 6	17	9 : 8	6.5 (0.4)	–

gave informed consent. Our comparison data come from the 73 typically developing 3-, 4-, 5-, and 6-year-olds previously reported (Nardini *et al.*, 2006; see Table 1). These control data are not reanalysed here, but we ask whether developmental trajectories in WS correspond to those previously described in the control groups, and whether WS groups attain the levels of performance of the control groups.

Apparatus

The array of hiding locations comprised 12 cups arranged on a green board measuring $82 \, \text{cm} \times 82 \, \text{cm}$, with toys which could potentially act as landmarks fixed along two of its edges (Figure 1a). Both the present WS data and the comparison control data (Nardini *et al.*, 2006) were collected in several different environments, including the Visual Development Unit at University College London and Oxford University, and quiet spaces provided by different schools (for the control data) and at a meeting of the Williams Syndrome Foundation UK (for the Williams data). In all these environments distant uncontrolled visual cues in the testing room (e.g. the stable framework of right-angled walls) could potentially act as external landmarks in those conditions in which the array was not moved. Although environments were not identical, all were sparsely furnished and predominantly empty, and shared the basic structure of right-angled walls likely to provide an external spatial framework (Gallistel, 1990). The board, landmarks, and hiding objects were identical for all participants. Two viewing positions were marked on the floor, each 20 cm from an edge of the board. The difference in viewing angle on the array between these positions was 135°. The hiding objects were small distinctive items such as toy animals and cars.

Design

Participant movement and array rotation varied by a 2×2 design that manipulated *body frame of reference* (available / not available) and *environment frame of reference* (available / not available). Before retrieval, participants

either walked to the other viewing position, or halfway and back to their initial position; the walking demand was therefore matched across conditions. At the same time, the array was either rotated by 135° relative to the room, or was not rotated. The four conditions are described in detail in Figure 1a and b.

There were four blocks of four trials, each block comprising one trial from every condition. The experiment lasted 15–20 minutes; greater numbers of trials would have made it unusable with our youngest controls (Nardini *et al.*, 2006), or the younger participants with WS. Condition orders and hiding locations were pseudorandomly generated for each participant. The cup nearest the centre of the board was not used because it was not sufficiently displaced by rotation. The remaining 11 locations each appeared at least once for each participant, but the same location was not repeated on successive trials, and overall, locations in different regions of the board appeared with equal frequency in different conditions. There were no practice trials, but conditions in the first block had a constant order (*neither-move, participant-move, array-move, both-move*), which introduced participants to the different demands of the task. Condition orders within the following three blocks were random.

Procedure

One experimenter hid objects and recorded responses while a second walked with the participant. On each trial, the first experimenter picked up one of the cups and placed the object in the space under it. The cup was lowered once the experimenters were sure that the participant had seen where it was. The second experimenter then walked with the participant, either around to the other viewing position, or halfway and back. A large sheet of card was held to one side of the participant's face to prevent them from fixating the array during the walking phase. On the *environment*-inconsistent conditions (*both-move* and *array-move*) the first experimenter also rotated the board during this part of the trial. In the search phase, participants tapped the top of a cup with a ruler to indicate where they thought the object was. The experimenters lifted the cup. If the search was incorrect, the participant was shown the correct location.

On the first rotation trial, the experimenters demonstrated how the board could be turned before the trial began. On subsequent rotation trials, participants were warned before they searched that the array had 'turned around', in order to rule out failure to understand that the array had been moved as a reason for incorrect search. On all trials other than the first rotation trial, participants did not know where they would be walking, and whether the array would be rotated or not, until the toy had been hidden and the walking phase had started. Each trial began at whichever viewing position the last had ended. This procedure is exactly the same as for Nardini *et al.*, 2006, and the lead experimenter was the same for both datasets.

Analysis

On each trial we recorded the first location searched. This was subsequently converted to distance (cm) from the correct cup, 0 cm corresponding to a correct search. For each trial this error distance was transformed into a standardized score as follows. Each hiding place has an average error expected by chance. This value, which would be obtained by a participant searching at random over many trials, is given by the mean of the distances between that place and all 12 possible search locations, including the correct one. Scores were calculated as 100 * (*chance distance – error distance*)/*chance distance*. Following this transformation, 100 corresponds to a correct search, while 0 corresponds to a search at a distance equal to chance. Values below 0 correspond to errors greater than the average expected by chance. A participant's overall score for each condition was calculated as the mean of their scores in that condition.

We used this parametric measure rather than percent correct, as it is a more robust measure of accuracy given a small number of trials (a participant's average per condition was based on only four trials). The parametric measure includes information about the size of participants' errors, whereas when scored as percent correct this error information is lost. The measure is equivalent across all locations, in that it is scaled against the differing expected levels of performance of a participant searching at random. (Before scaling, average errors in cm on random search would be smaller for locations close to the centre.) Scoring how far participants searched from a particular place also enables us to consider proximity to alternative predicted locations for search, places that are incorrect, but predicted by incorrect use of spatial frames of reference (see Results).

Our main analyses of performance in WS were by chronological age. An alternative approach would be to match WS and typically developing individuals on a measure of mental age such as our vocabulary measure. A difficulty with this approach is that while the majority of our WS sample have verbal ages above 6 years, typically developing children above 6 years and typical adults rapidly attain ceiling on the present test (Nardini, 2006), so the test becomes uninformative as it underestimates participants' ability and does not differentiate between conditions. However, we analyse the effect of mental age as indexed by our vocabulary measure in two ways: in ANOVAs that group participants by verbal age, and in regression analyses with verbal age as a predictor of performance.

Results

Figure 2a plots mean scores and 95% confidence intervals by condition for each WS chronological age group. In Figure 2b scores of adults and children with WS are replotted by median splits based on verbal age. Figure 2c replots comparison typically developing 3–6-year-old data from Nardini *et al.*, 2006.

As Figure 2a shows, groups with WS showed a marked impairment compared with chronologically much younger controls (Figure 2c). The oldest WS group, with age range 26–42 years, did not score above the typical 5-year-old group. All but the youngest WS group had mean verbal ages 7 years or higher (see Table 1); i.e. higher than the oldest control group. Therefore scores in WS are also clearly below expected norms when considered by verbal age. The chronological age 26–42 group was the only WS group to score significantly above chance on the *array-move* condition (see 95% confidence interval error bars), i.e. to show successful use of an array-based frame of reference. In typically developing children aged 3–6 years, performance showed a regular decrease across conditions, left to right, corresponding to independent, additive effects for the *body* and *environment* factors (Figure 2c). Most groups with WS also showed this regular pattern, with some exceptions (Figure 2a). A series of analyses examined development within WS, and comparisons between WS and control groups.

Development in WS by chronological age

An ANOVA examined the effects of the *body frame of reference* (available/not available), the *environment frame of reference* (available/not available), and *age group* (5–7/8–11/12–15/16–23/26–42), in the participants with WS. There were within-subjects effects for *body FoR* ($F(1, 40) = 11.7$, $p < .001$) corresponding to better recall when the *body FoR* was available and *environment FoR* ($F(1, 40) = 56.4$, $p < .001$), corresponding to better recall when the *environment FoR* was available, but no interaction between these ($F(1, 40) = 0.9$, $p > .3$). This shows that considered as a whole, the WS sample used both *body*- and *environment*-based frames of reference, and that these effects combined additively to improve recall accuracy, as they did in typically developing 3–6-year-olds (Nardini *et al.*, 2006; see Figure 2c).

The main effect of *age group* was not significant ($F(4) = 1.2$, $p > .3$). In other words, considering overall score across conditions, there was no significant advantage for chronologically older groups. This result stands in contrast to controls aged 3–6 years, who showed a strong *age* effect corresponding to rapid development of overall ability on the task (Nardini *et al.*, 2006). This can largely be attributed to improving ability in using the *array*-based reference frame, which can contribute to performance on all conditions.

In WS, neither the effect of having the *body* frame of reference available nor the effect of having the *environment* frame of reference available changed significantly as a function of *age group*; for *body FoR* × *age group*, $F(4, 40) = 1.6$, $p > .1$; for *environment FoR* × *age group*, $F(4, 40) = 1.3$, $p > .2$. The absence of a change in use of the *body* frame of reference with age corresponds to the pattern in controls, in whom advantages for *body*
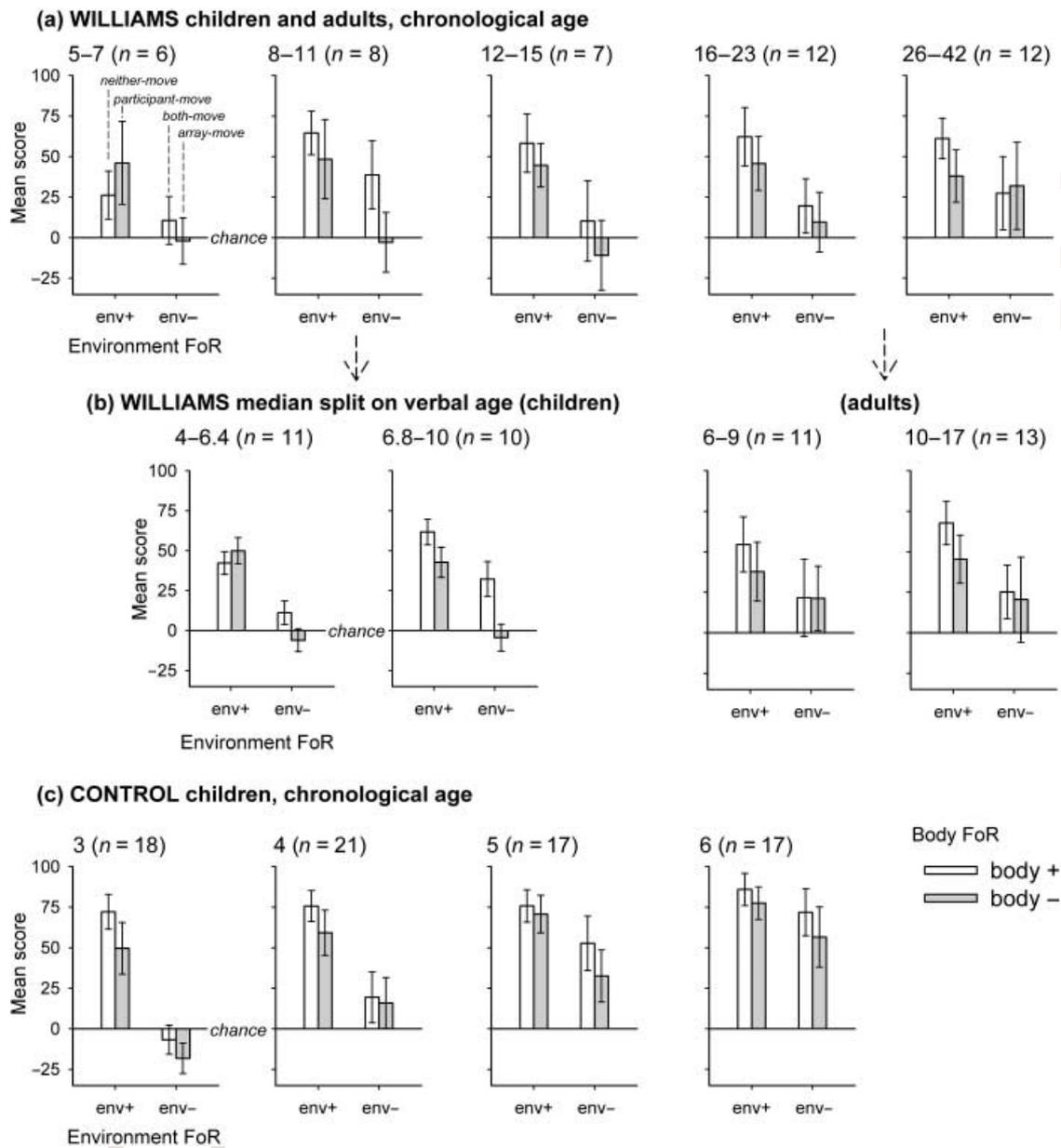
Figure 2 *Mean scores and 95% confidence intervals by group and condition, for (a) children and adults with Williams syndrome, divided by chronological age; (b) children and adults with Williams syndrome, divided by verbal age, and (c) typically developing 3–6-year-olds (replotted from Nardini et al., 2006). White bars: body FoR available. Grey bars: body FoR not available. Columns on the left: environment FoR available. Columns on the right: environment FoR not available. The order of conditions, left to right, is therefore* neither-move, participant-move, both-move, array-move, *as labelled in the top left plot.*

FoR-available trials did not change over the range 3–6 years. The absence of a change in the use of the *environment* frame of reference differs from the pattern in controls, who showed a strong improvement on the *environment FoR*-unavailable conditions with age (Figure 2c; reducing difference between left and right bars with age; Nardini *et al.*, 2006). In controls this corresponded to an emerging ability to solve *environment FoR*-unavailable conditions by use of the *array* frame of reference. The ongoing disadvantage for these conditions in older participants with WS corresponds to the lack of a reliable *array* frame of reference.

Also unlike typically developing 3–6-year-old groups, groups with WS showed a significant three-way interaction between *body FoR*, *environment FoR*, and *age group* ($F(4, 40) = 2.8$, $p < .05$). This interaction shows that the way in which *body* and *environment* frames of reference combined changed with age in WS, and reflects in the differences between patterns across conditions at different ages (Figure 2a). Whereas *body* and *environment* frames of reference appear independent and additive for the intermediate age groups, giving rise to an orderly pattern of descending performance across conditions (left to right at each age, Figure 2a), they show different patterns

for the youngest and oldest groups. The youngest WS group (Figure 2a) shows an unusual interaction between *body* and *environment FoRs*, where whether having a *body FoR* available or not has a positive or negative effect on performance depends on whether the *environment FoR* is available. This pattern may reflect a genuine aspect of young WS performance, but could arise from increased noise relative to the more orderly performance at older ages. The oldest WS group (Figure 2a) shows a different interaction that is also unlike the control pattern. Whereas in controls the two conditions with *environment FoR* not available (Figure 2c, bars on the right) are further differentiated by whether a *body FoR* was available (Figure 2c, white vs. grey bars on the right), the condition with neither showing least accuracy, in the oldest WS group there is no such difference (Figure 2a, right). Relative to controls, the profile across conditions is quite flat in the oldest WS group. Overall it is clear that while development in WS may have included changes in the pattern of performance across conditions (significant three-way *body FoR* × *environment FoR* × *age group* interaction), it did not include any significant overall improvement (no main effect of *age group*).

These results are replicated in just the subgroup of participants for whom we had confirmation of a positive result on the fluorescence in situ hybridization (FISH) test ($n = 23$). As in the analysis of all participants, there were within-subjects effects for *body FoR* (available/not available); $F(1, 17) = 5.5$, $p < .05$, corresponding to better recall when the *body FoR* was available, and for *environment FoR* (available/not available); $F(1, 17) = 46.4$, $p < .001$, corresponding to better recall when the *environment FoR* was available, and there was no interaction between these ($p > .6$). Likewise as in the main analysis, there was no main effect of *age group* ($F(4) = 2.2$, $p > .1$) and no interaction of *age group* with either *body FoR* or *environment FoR* ($p > .3$; $p > .1$). Unlike in the main analysis however, there was no three-way *body FoR* × *environment FoR* × *age group* interaction ($p > .1$), although this is not surprising given the much smaller numbers in each age group in this reanalysis. This analysis shows that the main features of the WS result are present in just those participants with a positive FISH test.

To provide the most sensitive test for effects of age on performance in individual conditions, each participant's chronological age was entered in a linear regression analysis against performance on each condition. Figure 3a plots scores on each condition by chronological age for participants with WS and controls. In controls aged 3 to 6 years, all but the baseline *neither-move* condition, in which the youngest participants already scored highly, showed dramatic development. In *neither-move*, development in WS was likewise not significant ($r^2 = .06$, $p > .1$). No development was discernible in WS for either the walking around test (*participant-move*, $r^2 = .02$, $p > .3$) or for *both-move* ($r^2 = .01$, $p > .4$), in contrast to controls who showed rapid development in both. The WS group did show a significant age improvement on the *array-move*

condition, dependent on using the array frame of reference; $r^2 = .14$, $p < .01$. However the shallow line corresponding to improvement on this task in WS stands in contrast to its rapid mastery by typical 3–6-year-olds (see plot).

Development in WS by verbal age

Adults with WS are very variable in cognitive outcome. Our vocabulary measure provides a test of their ability in a non-spatial domain. We analysed verbal age in two ways: as an alternative grouping factor (instead of chronological age) in ANOVA, and as an alternative regression term. For ANOVAs we divided into 'high' and 'low' verbal age by median splits separately for children (chronological age 5–15) and adults (16–42) with WS. For regression we analysed scores with the continuous range of verbal ages in the WS sample.

Figure 2b shows children with WS (total $n = 21$) and adults with WS (total $n = 24$), combined and re-divided by median verbal age (in adults the median, 10.8, was shared by two participants, leading to an 11:13 split). As Figure 2b shows, there is a small advantage for higher verbal age WS children, but little difference between the two verbal age adult groups. For children, an ANOVA with factors *body FoR* (available/not available), *environment FoR* (available/not available), and *verbal age group* (high/low) found no main effect of *verbal age group* ($F(1) = 1.3$, $p > .2$), a *verbal age group* × *body FoR* interaction ($F(1, 19) = 6.0$, $p < .05$), and no *verbal age group* × *environment FoR* interaction ($F(1, 19) = 0.2$, $p > .6$). Thus there was no overall advantage for the higher verbal age subgroup of WS children, but there was an advantage in those conditions allowing use of the *body* frame of reference (conditions *neither-move* and *both-move*; see raised performance on these, white bars in Figure 2b, left). For adults divided by verbal age, an ANOVA with these same factors found no main effect of *verbal age group* ($F(1) = 0.4$, $p > .5$), no *verbal age group* × *body FoR* or *verbal age group* × *environment FoR* interaction ($F(1, 22) = 0.2$, $p > .6$; $F(1, 22) = 0.4$, $p > .5$), and no three-way interaction ($F(1, 22) = 0.0$, $p > .9$). These results show that verbal age predicted to a degree WS children's ability to benefit from the body frame of reference (though not their overall performance), and did not predict either use of body or environment frames of reference, or overall performance, in WS adults.

To test for effects of verbal age on the four individual conditions, each participant's verbal age was entered into a regression against score. These analyses, which included the continuous range of verbal ages in the full sample of WS participants, are plotted in Figure 3b. Verbal age was a significant predictor of performance on the baseline condition *neither-move*; $r^2 = .10$, $p < .05$. Verbal age did not predict scores on *participant-move* ($r^2 = .01$, $p > .6$) or *both-move* ($r^2 = .01$, $p > .6$), and was marginally correlated with scores on *array-move* ($r^2 = .08$, $p = .056$). These results show that, for 5–42-year-olds with WS considered as a whole, the vocabulary measure
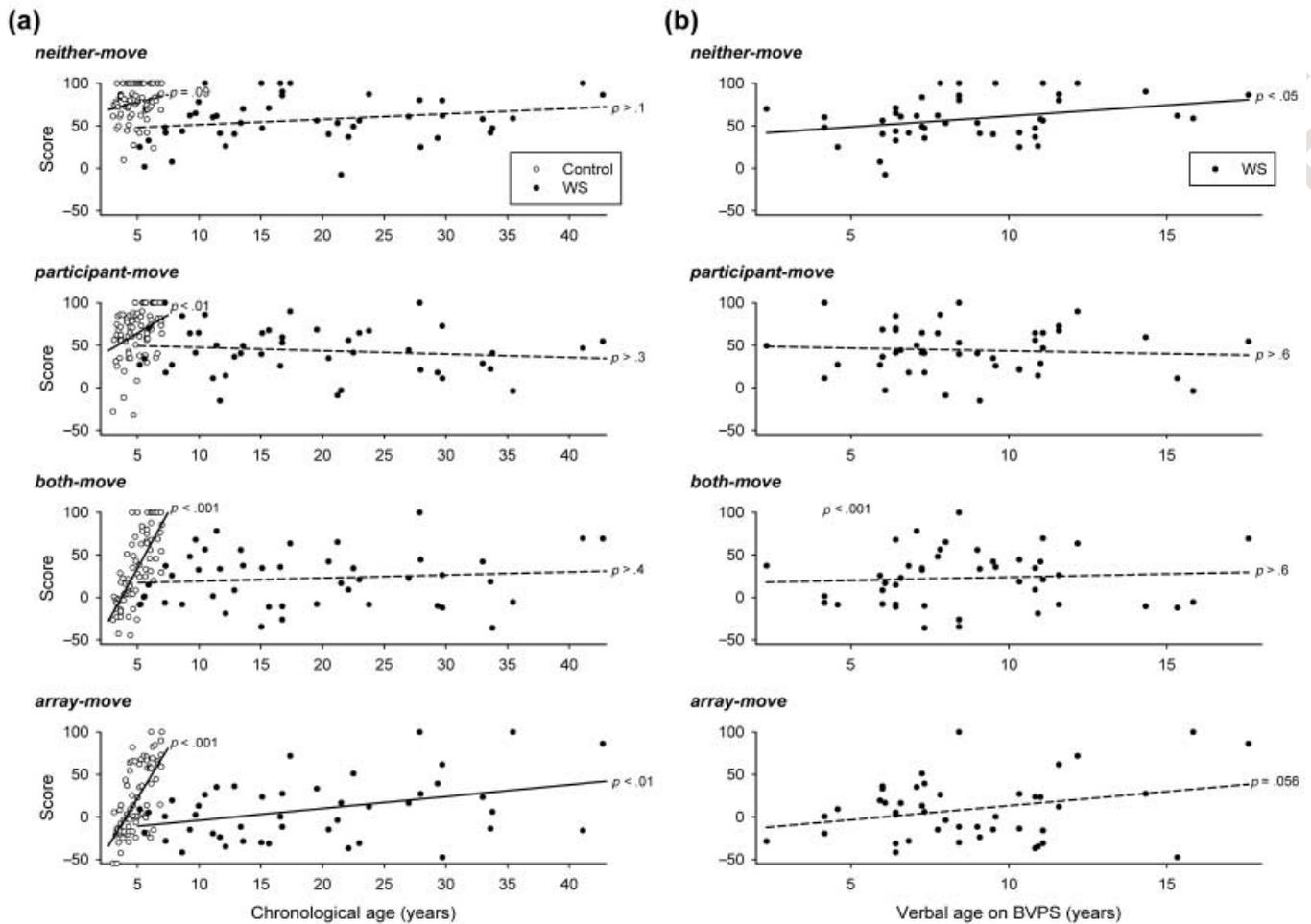
Figure 3 *Scores on each condition (a) by chronological age in typically developing (open circles) participants and those with WS (filled circles); (b) by verbal age in participants with WS. Regression line: linear regression significant (solid line); not significant (dashed line) at the 5% level; see* p-*values.*

was a predictor of performance on some elements of the test. Whereas *neither-move* was not significantly predicted by chronological age, it was predicted by verbal age. By contrast, *array-move*, the strongest test of landmark use, was predicted more strongly by chronological than by verbal age.

Comparisons between WS and typically developing groups

In Figure 2, several similarities and differences between individuals with WS and typically developing children are evident. First, even the chronologically oldest groups of participants with WS did not attain typical 5-year-old performance. Second, 16–23-year-olds with WS closely matched the profile for 4-year-olds, while 12–15-year-olds with WS closely matched the profile for 3- and 4-year-olds (appearing intermediate to these). These similarities suggest that individuals with WS use spatial frames of reference in similar ways to much younger controls.

A set of statistical comparisons was made to illustrate this overall pattern. To test whether the chronologically oldest groups with WS (16–23 and 26–42 years) were below the level of typical 5-year-olds, these were compared with ANOVAs. These had within-subjects factors *body FoR* and *environment FoR* (available/not available) as before, and between-subjects factor group (Control/ WS). In both the WS 16–23 *vs.* Control 5 and the WS 26–42 *vs.* Control 5 comparisons, there were highly significant effects of *group*, corresponding to an overall advantage for the typical 5-year-olds; in the comparison with 16–23s, $F(1) = 13.3$, $p < .001$; in the comparison with 26–42s, $F(1) = 32.6$, $p < .001$. There were no significant interactions including *group* in either case. These analyses show that overall, the two oldest groups with WS performed below the level of typical 5-year-olds.

An ANOVA tested whether the 16–23-year-old WS group differed from the typical 4-year-old group. The main effect of *group* was nonsignificant ($F(1) = 1.3$, $p > .2$), as were interactions between *group* and *environment FoR* ($F(1, 31) = 0.7$, $p > .3$), *group* and *body FoR* ($F(1, 31) = 0.1$,

1 $p > .7$), and the three-way interaction ($F(1, 31) = 0.2$,
2 $p > .6$). These low and nonsignificant F-values show little
3 evidence for differences between these WS and control
4 groups. When the oldest (26–42) WS and typical 4-year-
5 old group were compared, the main effect of *group* was
6 likewise nonsignificant ($F(1) = 0.12$, $p > .7$), as was the
7 *body FoR × group* interaction ($F(1, 31) = 0.0$, $p > .9$).
8 The *environment FoR × group* interaction was significant
9 ($F(1, 31) = 6.92$, $p < .05$) although the three-way inter-
10 action was not ($F(1, 31) = 0.7$, $p > .3$). Thus, in overall
11 performance the oldest WS group was comparable to
12 typical 4-year-olds (no main effect of *group*), but across
13 conditions this WS group showed a pattern that is not
14 usual for younger controls (*environment FoR × group*
15 interaction). The interaction corresponds to the relatively
16 weaker effect of *environment FoR* on performance in
17 the WS 26–42 group, seen in the more flat profile
18 across conditions relative to the typical 4-year-old group
19 (Figure 2).

20 In conclusion, WS individuals of chronological age
21 16–23 and 26–42 years scored significantly lower than
22 typical 5-year-olds. WS individuals aged 16–23 years did
23 not differ from typical 4-year-olds either in overall level
24 or in the pattern across conditions; those aged 26–42 did
25 not differ from 4-year-olds in overall level but did show
26 a subtly different pattern across conditions, the *environ-*
27 *ment FoR* predicting performance less strongly than it
28 did for 4-year-olds. Nonsignificant differences in these
29 comparisons should be interpreted with caution owing
30 to the small sizes of the WS groups, but the significant
31 differences in the comparisons with 5-year-olds show
32 clearly that the oldest WS groups were less accurate than
33 typical 5-year-olds.

Patterns of error in WS

37 We previously found that errors made by young controls
38 when the array rotated were consistent with use of
39 incorrect frames of reference (Nardini *et al.*, 2006). On
40 the *array-move* condition, in which neither *environment* nor
41 *body* frames of reference indicate the target's location
42 (see Figure 1b), typical 3-year-olds' searches were never-
43 theless closer than chance to the place predicted by
44 these reference frames, i.e. to the object's place in the
45 room before rotation (Nardini *et al.*, 2006). This shows
46 that while 3-year-olds failed to use the *array* frame of
47 reference to solve this condition, their responses were
48 not random, but corresponded to an incorrect selection
49 of (or failure to inhibit) the other reference frames. This
50 pattern of error was no longer seen at age 4 and above, as
51 participants' performance on the *array-move* condition
52 improved.

53 In the present WS sample, we measured how close
54 each search on an *array-move* trial was to the place pre-
55 dicted by the use of either *body* or *environment* frames of
56 reference, which both indicate the same incorrect search
57 location (the object's place prior to array rotation; see
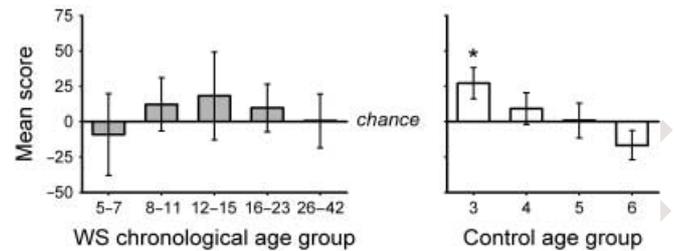58 Figure 1b). As in the main analysis, this distance was

Figure 4 *Performance on* array-move *trials scored in terms of searches' proximity to the location predicted by use of the either of the (incorrect) body- or environment-based frame of reference. Mean scores (95% c.i.s) reflect mean proximity to the incorrect location predicted by these reference frames (negative scores are further from the predicted location than the 'chance' level associated with random responding). Grey bars: WS groups. White bars: control groups (data replotted from Nardini* et al., *2006). '*': 95% c.i. excludes chance.*

transformed to a standard score scaled against the
average distance from this place expected by chance. Mean
scores on this measure are plotted in Figure 4. No WS
group's searches on *array-move* were closer, on average,
to this predicted place than would be expected by chance
(Figure 4, left: no 95% c.i. excludes chance). Thus there
was no WS group whose errors on *array-move* could be
explained by consistent incorrect use of *body* or *environ-*
ment frames of reference. This contrasts with the positive
result on this measure for typical 3-year-olds (replotted
for comparison, Figure 4, right). Therefore while very
young controls' failures on the *array-move* condition can
be explained by a consistent error (incorrect use of the
body and *environment* reference frames), errors in WS
groups in the present study could not be explained in the
same way. This may represent a higher rate of between-
subject or between-trial variations in strategy in the WS
group, relative to young controls, although the smaller
sizes of the WS groups also mean that the test has lower
statistical power.

As the target location changes from trial to trial, it
could be that errors in WS are due not just to errors in
spatial coding, but also to proactive memory interference
between trials. To address this possibility, we determined
whether either controls or participants with WS showed
any deterioration in performance over the course of the
study. We analysed scores on baseline condition *neither-*
move by block for the two groups. In the control group
an ANOVA found a significant linear effect of *block*
($F(1) = 7.2$, $p < .01$) corresponding to a decline in per-
formance over the course of the study. In the WS group
however, the linear effect of *block* was not significant
($F(1) = 0.7$, $p > .4$). Thus in control, but not WS groups,
performance fell reliably over the course of the study.
There is therefore no evidence that the low overall scores
in the WS group arose from a greater build-up of proactive
interference or fatigue as the study progressed.

Discussion

Overall, the development of spatial coding in Williams syndrome was slow and incomplete relative to controls. Importantly, although performance in the WS group was greatly delayed, it was not anomalous: considered as a whole, the WS sample showed independent, independently additive use of *body*- and *environment-based* spatial frames of reference, as typically developing children and adults do (Nardini *et al.*, 2006; Burgess *et al.*, 2004).

However, no WS group except the oldest demonstrated an ability to use an *array-based* frame of reference, necessary to solve the *array-move* condition. Regression analysis showed that ability on the *array-move* condition improved significantly in WS over the range 5 to 42 years, but even in the oldest group this ability was marginal. In typical development, the emerging ability to solve the *array-move* condition is accompanied by a rapid improvement over all conditions. It is likely that representing locations using the array frame of reference (in terms of local landmarks within the array, and the array's overall layout) contributes to this overall improvement. Therefore the 'arrested' level of performance in WS across all conditions may be explained by their profound difficulties in using this reference frame. Analogous conditions are the most difficult for typical children (Huttenlocher & Presson, 1973; Nardini *et al.*, 2006) and adults (Simons & Wang, 1998; Burgess *et al.*, 2004). Young typically developing children who have not yet mastered the *array* frame of reference combine *body* and *environment* frames effectively when these are available (Nardini *et al.*, 2006). In the present study individuals with WS aged 12–15 and 16–23 years closely followed these patterns of performance, seen at control ages 3 and 4 years.

A further component in ability to use the array frame of reference to solve the *array-move* condition may be inhibition of the incorrect body- and environment-based frames of reference. Ability to inhibit a prepotent response develops over the age range in which our control group mastered the task (Gerstadt, Hong & Diamond, 1994), and children with Williams syndrome show deficits on inhibition tasks, particularly those with spatially directed responses (Atkinson *et al.*, 2003). The WS deficit in using local landmarks is therefore also consistent with an inhibition or response selection impairment. A further route to solving the *array-move* condition could be mental rotation of the array. Individuals with WS are impaired on mental rotation tasks (Farran, Jarrold & Gathercole, 2001), so the impairment in the present groups is also consistent with impaired ability for mental manipulation of the array.

Unlike typically developing 3–6-year-olds, the WS sample showed a three-way *age group* × *body FoR* × *environment FoR* interaction, which indicates some developmental reweighting of how the *body* and *environment* factors combined. This is reflected in the unusual patterns, relative to controls, in the youngest and oldest WS groups (Figure 2). Thus in the youngest WS group there was no overall advantage for conditions allowing recall using a *body-based* frame of reference. This pattern could be anomalous, or it could correspond to a developmental stage that is usual for control ages younger than 3 years. In a statistical comparison with typical 4-year-olds, the oldest WS group showed a reduced effect of the *environment* frame of reference on recall accuracy. The flatter profile across conditions in the oldest WS group shows that performance differences across conditions are less well predicted by the spatial frames of reference available than in typical children. The oldest WS group's deficits may therefore include performance or memory limitations common to all conditions. By contrast, younger adults with WS showed a striking similarity to the typical 4-year-old pattern, and did not differ from the 4-year-old pattern in statistical comparison. These results are partly consistent with the hypothesis that visuospatial impairments in WS can be understood in terms of a developmental 'arrest' (Landau & Hoffman, 2007), but also show that aspects of performance in older groups can be unusual relative to young controls.

Whether WS children or adults were above or below median verbal age did not predict overall performance on the task, although among children with WS those with a higher verbal age performed better on conditions with a *body* frame of reference available. In regression analyses of verbal age in the whole sample of 5–42-year-old individuals with WS, verbal age was a significant and better predictor of performance on baseline condition *neither-move* than chronological age. Verbal age did not significantly predict performance on any other condition, including the test for use of an *array* frame of reference, *array-move*, which was significantly and more strongly correlated with chronological age. Overall these results indicate that the development of spatial frames of reference across the lifespan in WS did not predominantly depend on cognitive development as indexed by verbal age.

There was, however, considerable variability in performance in WS (see error bars, Figure 2a), some of which may be accounted for by differences in overall development of mental age. In future, a test that scaled up to remain below ceiling for mental age-matched controls would enable WS individuals to be compared directly with age-matched controls, and their impairment relative to these could be quantified. In the present case, WS groups clearly showed a considerable impairment relative to verbal age, considering that all but the youngest WS group had mean verbal age 7 years or greater, yet even the oldest groups performed below the typically developing 5-year-old level. The finding of a profound impairment on this visuospatial task relative to both chronological and verbal age is highly consistent with the WS cognitive profile (Bellugi *et al.*, 1990; Atkinson *et al.*, 2001).

The better prediction of *array-move* performance (the strongest test of landmark use) by chronological than verbal age suggests that use of landmarks in the task did

not crucially depend on a verbal coding strategy. How-ever, as our vocabulary measure was not specifically a test of spatial language, it could still be that the WS deficit reflects a failure to verbalize the task. Two pre-vious results speak to this (Nardini *et al.*, 2006; Nardini, 2006). First, in our earlier study, those typical 5- and 6-year-olds who could not describe the hiding places were still above chance on the test of viewpoint independent recall, *array-move*, which shows that it is possible to encode the places relative to landmarks without using language (Nardini *et al.*, 2006). Second, when typical adults did the task while performing verbal shadowing which prevented them from using language to remember the locations, they still scored much higher than typical 6-year-olds (Nardini, 2006), and therefore also higher than the WS participants in the present study. These results indicate that ability to use landmarks in the present task does not depend entirely on verbal strategies in typically developing participants. The WS deficit therefore cannot be attributed entirely to the absence of a verbal strategy.

Unlike the 3-year-old control group, no WS group showed a pattern of recall using the *array* frame of reference alone (condition *array-move*) that could be explained by consistent selection of the incorrect reference frame or frames. This suggests that causes of error in the WS groups were more variable than in young typically developing children. It may also be that such consistency as there was in the WS groups' errors was not detectable owing to the relatively small group sizes. Impaired spatial recall in WS relative to controls was not explained by greater proactive memory interference or fatigue. Whereas controls showed reliable deterioration in performance on the baseline condition over the course of the study, participants with WS scored low throughout but did not deteriorate.

As outlined in the introduction, use of the spatial frames of reference manipulated in the present study depends on several distinct kinds of representations, subserved by different neural systems. The most important results to consider in terms of neural processing are the overall impairment in WS (including in basic localization, when neither observer nor target change position), and the highly impaired use of an intrinsic (*array*) frame of reference.

The profound delay in spatial recall even for the simple case where neither the participant nor the target change position (condition *neither-move*) is consistent with a dorsal-stream deficit in WS (Atkinson *et al.*, 1997; Meyer-Lindenberg *et al.*, 2004). Additional impairments in use of visual landmarks to code locations in an intrinsic (*array*) frame of reference may also contribute to the basic localization deficit. We suggest that in typical development, improvements in basic localization depend partly on increasingly proficient coding of objects relative to local landmarks (array-based frame of reference), which contributes additively to recall across conditions. The highly impaired use of an intrinsic (*array*) frame of reference in WS may therefore partly explain the

persistent deficits even in basic localization, when neither observer nor target move.

Viewpoint-independent codings relative to landmarks, which would facilitate use of an *array* frame of reference in the present task, are associated with the hippocampus (King, Burgess, Hartley, Vargha-Khadem & O'Keefe, 2002; Ekstrom, Kahana, Caplan, Fields, Isham, Newman & Fried, 2003). The deficit in participants with Williams syndrome is therefore consistent with their structural and functional hippocampal abnormalities (Meyer-Lindenberg *et al.*, 2005).

To summarize, individuals with WS of all ages were severely impaired on this spatial memory task. A relative strength in the WS group, at all ages but the youngest, was in combining *body* and *environment* frames of reference when these were available. A major deficit was found in use of a frame of reference based on local landmarks within the array. This could account for a large part of the WS spatial deficit. The deficit may be specifically in coding relative to these landmarks, in selecting this coding in preference to those based on other frames of reference, or in adopting the array frame of reference for mental manipulation (rotation) of the array.

The extent to which results from the present task gen-eralize to larger scale navigation is an important further question. It would be interesting to vary the local and environment landmarks in order to determine to what degree additional landmarks improve performance on basic localization tasks in typical development, and to what degree the WS deficit on such tasks can be accounted for by a failure to profit from these. It is also possible that participants with WS would perform better given a simpler display with fewer landmarks. The roles of allocentric coding and inhibition in viewpoint-independent recall, and their relative impairments in WS, are also important questions for further research.

Acknowledgements

References

Atkinson, J., Anker, S., Braddick, O., Nokes, L., & Mason, A. (2001). Visual and visuospatial development in young children with Williams syndrome. *Developmental Medicine and Child Neurology*, **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. *Developmental Neuropsychology*, **23**, 139–172.

Atkinson, J., Braddick, O., Anker, S., Ehrlich, D., Macpherson, F., & Rae, S. (1996). Development of sensory, perceptual, and cognitive vision and visual attention in young Williams syndrome children. Presentation at the Seventh International Professional Conference on Williams Syndrome, King of Prussia, PA.

Atkinson, J., Braddick, O., Rose, F.E., Searcy, Y.M., Wattam-Bell, J., & Bellugi, U. (2006). Dorsal-stream motion processing deficits persist into adulthood in Williams syndrome. *Neuropsychologia*, **44**, 828–833.

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**, 1922.

Bellugi, U., Bihrle, A., Jernigan, T., Trauner, D., & Doherty, S. (1990). Neuropsychological, neurological, and neuroanatomical profile of Williams syndrome. *American Journal of Medical Genetics*, **6**, 115–125.

Burgess, N., Maguire, E.A., & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron*, **35**, 625–641.

Burgess, N., Spiers, H.J., & Paleologou, E. (2004). Orientational manoeuvres in the dark: dissociating allocentric and egocentric influences on spatial memory. *Cognition*, **94**, 149–166.

Dilks, D.D., Hoffman, J.E., & Landau, B. (in press). Vision for perception and vision for action: normal and unusual development. *Developmental Science*.

Donnai, D., & Karmiloff-Smith, A. (2000). Williams syndrome: from genotype through to the cognitive phenotype. *American Journal of Medical Genetics*, **97**, 164–171.

Dunn, L.M. (1997). *British Picture Vocabulary Scale*. Windsor: NFER-Nelson.

Eckert, M.A., Hu, D., Eliez, S., Bellugi, U., Galaburda, A., Korenberg, J., Mills, D., & Reiss, A.L. (2005). Evidence for superior parietal impairment in Williams syndrome. *Neurology*, **64**, 152–153.

Ekstrom, A.D., Kahana, M.J., Caplan, J.B., Fields, T.A., Isham, E.A., Newman, E.L., & Fried, I. (2003). Cellular networks underlying human spatial navigation. *Nature*, **425**, 184–188.

Ewart, A.K., Morris, C.A., Atkinson, D., Jin, W., Sternes, K., Spallone, P., Stock, A.D., Leppert, M., & Keating, M.T. (1993). Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. *Nature Genetics*, **5**, 11–16.

Farran, E.K., & Jarrold, C. (2005). Evidence for unusual spatial location coding in Williams syndrome: an explanation for the local bias in visuo-spatial construction tasks? *Brain and Cognition*, **59**, 159–172.

Farran, E.K., Jarrold, C., & Gathercole, S.E. (2001). Block design performance in the Williams syndrome phenotype: a problem with mental imagery? *Journal of Child Psychology and Psychiatry and Allied Disciplines*, **42**, 719–728.

Farran, E.K., Tranter, L., Blades, M., & Boucher, J. (2007). Can individuals with Williams syndrome learn a route? Route knowledge and relational knowledge in a real world environment. Poster Presented at the Meething of the Society of Research in Child Development, Boston, MA.

Gallistel, C.R. (1990). *The organization of learning*. Cambridge, MA: MIT Press.

Gerstadt, C.L., Hong, Y.J., & Diamond, A. (1994). The relationship between cognition and action – performance of children $3\frac{1}{2}$–7 years old on a Stroop-like day-night test. *Cognition*, **53**, 129–153.

Greenberg, F. (1990). Williams syndrome professional symposium. *American Journal of Medical Genetics*, **6**, 85–88.

Henderson, S.E., & Sugden, D.A. (1992). *Movement Assessment Battery for Children*. London: The Psychological Corporation.

Huttenlocher, J., & Presson, C.C. (1973). Mental rotation and the perspective problem. *Cognitive Psychology*, **4**, 277–299.

King, J., Burgess, N., Hartley, T., Vargha-Khadem, F., & O'Keefe, J. (2002). Human hippocampus and viewpoint dependence in spatial memory. *Hippocampus*, **12**, 811–820.

Kippenhan, J.S., Olsen, R.K., Mervis, C.B., Morris, C.A., Kohn, P., Lindenberg, A.M., & Berman, K.F. (2005). Genetic contributions to human gyrification: sulcal morphometry in Williams syndrome. *Journal of Neuroscience*, **25**, 7840–7846.

Lakusta, L., Dessalegn, B., & Landau, B. (2006). Failure to represent geometry in people with Williams syndrome? Paper Presented at 47th Annual Meeting of the Psychonomic Society, November, 2006, Houston, TX.

Landau, B. & Hoffman, J.E. (2005). Parallels between spatial cognition and spatial language: evidence from Williams syndrome. *Journal of Memory and Language*, **53**, 163–185.

Landau, B., Hoffman, J.E., & Kurz, N. (2006). Object recognition with severe spatial deficits in Williams syndrome: sparing and breakdown. *Cognition*, **100**, 483–510.

Landau, B.L., & Hoffman, J.E. (2007). Explaining selective spatial breakdown in Williams syndrome: four principles of normal spatial development and why they matter. In J.M. Plumert & J.P. Spencer (Eds.), *The emerging spatial mind*. Oxford: Oxford University Press.

Meyer-Lindenberg, A., Kohn, P., Mervis, C.B., Kippenhan, S., Olsen, R.K., Morris, C.A., & Berman, K.F. (2004). Neural basis of genetically determined visuospatial construction deficit in Williams syndrome. *Neuron*, **43**, 623–631.

Meyer-Lindenberg, A., Mervis, C.B., & Berman, K.F. (2006). Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour. *Nature Reviews Neuroscience*, **7**, 380–393.

Meyer-Lindenberg, A., Mervis, C.B., Sarpal, D., Koch, P., Steele, S., Kohn, P., Marenco, S., Morris, C.A., Das, S., Kippenhan, S., Mattay, V.S., Weinberger, D.R., & Berman, K.F. (2005). Functional, structural, and metabolic abnormalities of the hippocampal formation in Williams syndrome. *Journal of Clinical Investigation*, **115**, 1888–1895.

Milner, A.D., & Goodale, M.A. (1995). *The visual brain in action*. Oxford: Oxford University Press.

Nardini, M. (2006). Components of spatial memory: a developmental analysis. PhD Thesis, University of London.

Nardini, M., Burgess, N., Breckenridge, K., & Atkinson, J. (2006). Differential developmental trajectories for egocentric, environmental and intrinsic frames of reference in spatial memory. *Cognition*, **101**, 153–172.

O'Hearn, K., Landau, B., & Hoffman, J.E. (2005). Multiple object tracking in people with Williams syndrome and in normally developing children. *Psychological Science*, **16**, 905–912.

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

Reiss, A.L., Eckert, M.A., Rose, F.E., Karchemskiy, A., Kesler, S., Chang, M., Reynolds, M.F., Kwon, H., & Galaburda, A. (2004). An experiment of nature: brain anatomy parallels

cognition and behavior in Williams syndrome. *Journal of Neuroscience*, **24**, 5009–5015.

Reiss, J.E., Hoffman, J.E., & Landau, B. (2005). Motion processing specialization in Williams syndrome. *Vision Research*, **45**, 3379–3390.

Simons, D.J., & Wang, R.F. (1998). Perceiving real-world viewpoint changes. *Psychological Science*, **9**, 315–320.

Smith, A.D., Gilchrist, I.D., Hood, B.M., & Karmiloff-Smith, A. (2006). Developmental components of large scale search: evidence from children and individuals with partial genetic deletions. *Cognitive Processing*, **7** (Suppl. 1), S93–S94.

Stromme, P., Bjornstad, P.G., & Ramstad, K. (2002). Prevalence estimation of Williams syndrome. *Journal of Child Neurology*, **17**, 269–271.

Tager-Flusberg, H., Plesa-Skwerer, D., Faja, S., & Joseph, R.M. (2003). People with Williams syndrome process faces holistically. *Cognition*, **89**, 11–24.

Ungerleider, L.G., & Mishkin, M. (1982). Two cortical visual systems. In M.A. Goodale & R.J.W. Mansfield (Eds.), *Analysis of visual behavior* (pp. 549–586). Cambridge, MA: MIT Press.

Vicari, S., Bellucci, S., & Carlesimo, G.A. (2005). Visual and spatial long-term memory: differential pattern of impairments in Williams and Down syndromes. *Developmental Medicine and Child Neurology*, **47**, 305–311.

Vicari, S., Bellucci, S., & Carlesimo, G.A. (2006). Evidence from two genetic syndromes for the independence of spatial and visual working memory. *Developmental Medicine and Child Neurology*, **48**, 126–131.

Wang, P.P., & Bellugi, U. (1994). Evidence from two genetic syndromes for a dissociation between verbal and visual-spatial short-term-memory. *Journal of Clinical and Experimental Neuropsychology*, **16**, 317–322.

Wang, P.P., Doherty, S., Rourke, S.B., & Bellugi, U. (1995). Unique profile of visuo-perceptual skills in a genetic syndrome. *Brain and Cognition*, **29**, 54–65.

Wang, R.F., & Simons, D.J. (1999). Active and passive scene recognition. *Cognition*, **70**, 191–210.

MARKED PROOF

Please correct and return this set

Please use the proof correction marks shown below for all alterations and corrections. If you wish to return your proof by fax you should ensure that all amendments are written clearly in dark ink and are made well within the page margins.

Instruction to printer	Textual mark	Marginal mark
Leave unchanged	••• under matter to remain	⊘
Insert in text the matter indicated in the margin	⋏	New matter followed by ⋏ or ⋏⊗
Delete	/ through single character, rule or underline or ⊢——⊣ through all characters to be deleted	⌀ or ⌀⊗
Substitute character or substitute part of one or more word(s)	/ through letter or ⊢——⊣ through characters	new character / or new characters /
Change to italics	— under matter to be changed	⌣
Change to capitals	≡ under matter to be changed	≡
Change to small capitals	= under matter to be changed	=
Change to bold type	∿ under matter to be changed	∿
Change to bold italic	≈ under matter to be changed	≈
Change to lower case	Encircle matter to be changed	≢
Change italic to upright type	(As above)	⊥
Change bold to non-bold type	(As above)	⊥
Insert 'superior' character	/ through character or ⋏ where required	Ɏ or Ⴟ under character e.g. Ɏ or Ⴟ
Insert 'inferior' character	(As above)	⋏ over character e.g. ⋏
Insert full stop	(As above)	⊙
Insert comma	(As above)	,
Insert single quotation marks	(As above)	Ɏ or Ⴟ and/or Ɏ or Ⴟ
Insert double quotation marks	(As above)	Ɏ or Ⴟ and/or Ɏ or Ⴟ
Insert hyphen	(As above)	⊢⊣
Start new paragraph	⌐	⌐
No new paragraph	↪	↪
Transpose	⊔⊓	⊔⊓
Close up	linking ‿ characters	◠ ◡
Insert or substitute space between characters or words	/ through character or ⋏ where required	Ⴤ
Reduce space between characters or words	│ between characters or words affected	↑