
Inefficient search of large-scale space in Williams syndrome: Further insights on the role of LIMK1 deletion in deficits of spatial cognition

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Abstract. Williams syndrome (WS) is a genetic disorder associated with impairments of spatial cognition. This has primarily been studied in small-scale space, and rarely in large-scale environments. In order to fully characterise the spatial deficits in WS, and also to address claims that the deletion of LIM-kinase1 (LIMK1) on chromosome 7 is responsible for those deficits, we report an automated large-scale search task for humans that places the participant egocentrically within the search space. Search locations were defined as lights and switches embedded in the floor, and participants attempted to locate a hidden target by pressing the switch at potential locations. We compared individuals with WS to patients with smaller deletions (including LIMK1) in the critical region on chromosome 7. Whilst partial-deletion participants performed efficiently on the task, participants with WS demonstrated inefficient search profiles: their search slopes were steeper and they made significantly more erroneous revisits to previously inspected locations. Our findings indicate that spatial deficits associated with WS also affect large-scale spatial processing and suggest that hemizygous deletion of LIMK1 is not sufficient to account for any of the spatial deficits associated with WS.

1 Introduction

Williams syndrome (WS) is a rare multi-system neurodevelopmental disorder with associated cardiac, craniofacial, and growth abnormalities, caused by a hemizygous microdeletion of some 28 genes on chromosome 7q11.23, including elastin (ELN) and LIM-kinase1 (LIMK1) (Donnai and Karmiloff-Smith 2000; Frangiskakis et al 1996; Meyer-Linenberg et al 2006). The genetic deletion in WS results in an uneven profile of relatively proficient language alongside serious deficits in spatial perception and cognition (Bellugi et al 1994; Donnai and Karmiloff-Smith 2000). Reported spatial deficits have included local biases in constructional tasks (Georgopoulos et al 2004), impairments in spatial working memory (Vicari et al 2005), and difficulties with the manipulation of visual mental images (Farran et al 2001).

In order to determine how the presentation of spatial deficits corresponds to the WS genotype, researchers have made use of very rare cases of individuals with isolated deletions in the WS critical region, but not sufficient to cause the full-blown disorder. Studies of two families, some of whose members were hemizygous only for LIMK1 and ELN, indicated that a proportion of family members with these deletions displayed spatial impairments on constructional tests, whereas family members without the deletions did not (Frangiskakis et al 1996). A subsequent LIMK1 knockout mouse model yielded spatial deficits in the Morris water maze (Meng et al 2002). The combined findings seem to suggest that LIMK1 plays an important role in spatial cognition, and that its deletion leads to the serious spatial impairments in WS. However, this has

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been challenged by reports of four patients with partial deletions in the WS critical region (all hemizygous for LIMK1) (Karmiloff-Smith et al 2003a; Tassabehji et al 1999), none of whom demonstrated any spatial deficits on the same tests used by the earlier researchers. Subsequently, two of these individuals were investigated in a detailed case study, with neuropsychological tasks specifically designed to pinpoint the existence of subtle spatial impairments (Gray et al 2006). This included tests of spatial perception (eg orientation matching), memory (eg for location information), and construction (eg block design). Participants with partial deletions did not display any spatial deficits of the tasks, whereas individuals with WS were found to score significantly below the published norms.

A key issue here is that the spatial deficits described in the LIMK1 knockout mouse involved behaviours in which the animal must represent the changing position of its body in large-scale space, whereas the human tasks involve manipulations of objects in small-scale space, with the participant seated at a table. It is therefore possible that LIMK1 contributes to the representation of space for navigation but not to object-oriented spatial construction, especially given neuropsychological dissociations of these two forms of cognition (Aguirre and D'Esposito 1999; Guariglia et al 2005; Maguire and Cipolotti 1998; Spiers et al 2001). More fundamentally, there have been no published reports of WS spatial behaviour in a large-scale context, although some data suggest that individuals with WS may display navigational impairments (Nardini et al, in press; Tranter et al 2006). If we are to fully characterise the WS cognitive profile, then we must study spatial behaviour within a greater range of scales in which humans function. Therefore, in the present study we describe a task that measures the spatial behaviour of individuals with WS in a large-scale environment, in order to examine whether deficits extend to extrapersonal space.

Testing took place in a large-scale search apparatus, consisting of an array of search locations embedded in a floor (see Smith et al 2005). Participants walked around the array searching for a hidden target (a red light) by activating a switch at each potential target location (indicated by green lights). We tested two individuals with partial deletions (PD) of LIMK1 and ELN only (previously reported by Gray et al 2006; Karmiloff-Smith et al 2003a; Tassabehji et al 1999). By comparing the performance of these very rare individuals to that of two adults with full-blown WS we were able to address the question whether the deletion of LIMK1 alone is responsible for spatial deficits in the present large-scale context.

2 Method

2.1 Participants

We tested two individuals (WS1, WS2) with full WS deletions in the critical region (verified clinically and genetically by fluorescence in-situ hybridization) and two individuals with partial deletions of ELN and LIMK1 in the WS critical region (PD1, PD2). PD1 was a 35-year-old Caucasian male with SVAS; PD2, the brother of PD1, was a 41-year-old Caucasian male with supravalvular aortic stenosis (SVAS) (previously referred to as PM and TM, respectively—Gray et al 2006; Tassabehji et al 1999). WS1 (aged 18 years) and WS2 (aged 37 years) were both adult males with WS. Scores on tests of intelligence (British Abilities Scale: BAS II—Elliot 1997), spatial memory (Corsi block span), and construction (Rey figure and block design tests) are presented in table 1.

2.2 Apparatus

The apparatus (previously described by Smith et al 2005) comprised an isolated square room (4 m × 4 m × 2.5 m) with a raised platform floor. Embedded in the floor was a grid of 49 possible search locations, each consisting of two lights (one green, one red) and a switch positioned between them. The room was without any obvious landmarks

Table 1. Scores on standardised tests of intelligence and spatial processing (totals in parentheses) for WS and PD participants. Also tabulated are slope and intercept data from regression analyses of search time, and revisit data expressed as a percentage of the total number of button presses.

	Williams syndrome		Partial deletion	
	WS1	WS2	PD1	PD2
<i>Standardised tests</i>				
BAS verbal IQ	58	79	96	98
BAS spatial IQ	51	49	100	88
Corsi span	3	3	6	6
Rey figure (36)	10	18.5	29	34
Block design (13)	–	–	12	10
<i>Search functions</i>				
slope/s per item	3.09	1.36	0.92	0.81
slope 95% CI	0.80–5.36	0.47–2.25	0.59–1.24	0.43–1.19
intercept/s	–4.72	4.29	2.96	2.51
intercept 95% CI	–35.9–26.5	–7.90–16.5	–1.55–7.48	–2.71–7.74
<i>Revisits</i>				
5 items	0	11.11	0	0
10 items	0	2.22	0	0
15 items	1.22	9.09	0	0
20 items	13.89	1.42	0	0



Figure 1. The large-scale search laboratory: participants inspect potential target locations by activating the switch.

and completely surrounded by a dark blue curtain (see figure 1). The floor was controlled by personal computers in an adjoining room, which also recorded (with millisecond accuracy) the timing and location of each button press. The experimenter triggered each trial from this location and observed participants' performance with a closed-circuit camera discretely mounted in the laboratory.

2.3 Design and procedure

In a single trial, a randomised array of search locations was indicated by the green lights. Participants were required to search for the target by pressing the switch at each green-lit location until they had located the one that illuminated the adjacent red light (the target). Participants performed 28 search trials, comprising 7 trials of each

display size: 5, 10, 15, 20 (lit search locations). The order of trial presentation was fully randomised across display sizes for every participant. There were no predictable cues where the target would be, although its location was constrained such that each row and column of the grid was used. Once the target was located, all lights were extinguished and the next trial began. Participants started each trial from the same fixed location: the middle point of a perimeter row, with their back to the wall. The next trial was triggered once participants had returned to this location and were observing the room before them. The selection of this starting position was to ensure that the full display could be observed by participants at the start of each trial, as with a central fixation point in visual-search tasks.

3 Results

All participants completed the full number of trials. Mean search times for each participant (to activate the switch at the target location) are illustrated in figure 2 as a function of set size. The data for each individual were entered into a linear regression model. WS1 and WS2 demonstrated reliably different search performance compared with PD1 and PD2, revealed through slope and intercept data (presented in table 1). Slopes for PD1 and PD2 were 0.915 s/item (intercept: 2.97 s) and 0.813 s/item (intercept: 2.52 s), respectively. In comparison, participants with WS produced steeper search slopes: WS1 produced a search slope of 3.09 s/item, with an intercept of -4.72 s, and WS2 produced a search slope of 1.36 s/item, with an intercept of 4.29 s. Furthermore, participants with WS demonstrated greater variability in their search, as evidenced by the increased range of 95% confidence intervals for these measures (see table 1).

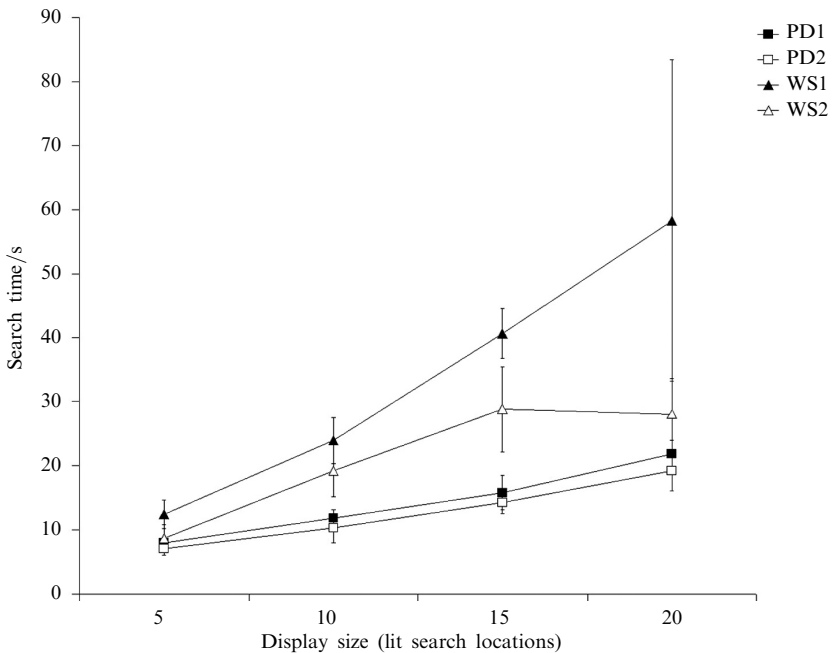


Figure 2. Search times to locate the target, as a function of display size. Bars represent standard error of the mean.

We have recently published large-scale search data from a sample of twenty-four healthy adults with a mean age of 20 years (Smith et al 2008). In one condition of that experiment the same task was used as that which is presented here, with participants also completing the same number of trials. The mean search slope for these individuals

was 789 ms/item, with an intercept of 4011 ms. Search times were entered into an analysis of variance with the present data, revealing a main effect of participant group ($F_{2,18} = 19.8$, $p < 0.001$). A posteriori Tukey tests showed that the participants with WS had significantly slower search times than control participants ($p < 0.001$) and PD individuals ($p < 0.001$). There was no significant difference between controls and PD1 and PD2.

These latency differences were primarily due to individuals with WS making more erroneous revisits to locations that they had already checked within a trial. Note that the PD participants made no revisits at all throughout the experiment. WS1 made significantly more revisits than PD1 (Fisher's Exact $p = 0.02$) and PD2 (Fisher's Exact $p = 0.02$), as did WS2 (Fisher's Exact $p = 0.05$ for both comparisons). As is apparent from table 1, these errors occurred for all display sizes: whereas WS1 made the most revisits when there were 20 locations to inspect, WS2 made his highest number even when there were only 5 locations to inspect. Typical adults from the Smith et al (2008) study made few revisits overall, with fourteen of them making no revisits at all. WS1 and WS2 both made significantly more revisits than the unimpaired control rate ($t = 2.23$ and 2.93 respectively, calculated by the method described by Crawford and Garthwaite 2002).

4 Discussion

Despite deletion of ELN and LIMK1, neither PD1 nor PD2 showed any deficits in the task. They made no erroneous revisits to previously inspected locations, and their search times were equivalent to data from healthy adults (Smith et al 2008). This result is consistent with the lack of PD impairment on object-oriented spatial construction tasks (Gray et al 2006; Karmiloff-Smith et al 2003a; Tassabehji et al 1999) and further implies that LIMK1 is not the major cause of spatial deficits in WS. In comparison with the PD individuals, both participants with WS demonstrated impairments in the search task, with significantly elevated latencies and more erroneous revisits. This therefore suggests that the deletion of LIMK1 alone does not affect large-scale spatial behaviour, at least in the context of egocentric search. In contrast, individuals with WS did display significantly inefficient search behaviour, which implies that additional deletions in the WS genotype, perhaps in the CYLN2-NCF1 region at the telomeric end of the WS critical region in chromosome 7q11.23, are important contributors to deficits of spatial cognition (see Karmiloff-Smith et al 2003a).

Previous research (Frangiskakis et al 1996; Meng et al 2002) had explicitly implicated the LIMK1 gene in deficits of spatial perception and cognition, and the rare opportunity to test PD cases such as those reported here allows us to critically evaluate those assertions. The present findings represent a key extension of the Gray et al (2006) case report, demonstrating that, along with unimpaired spatial abilities in small-scale contexts, PD1 and PD2 do not present any large-scale spatial impairments, compared with full-blown WS. This difference is also clear from the standardised test data presented in table 1. Spatial deficits have been described as a key feature of the WS cognitive profile (Bellugi et al 1994), although previous observations have only been within a small-scale allocentric or object-oriented context. Although navigational impairments in WS have been suggested elsewhere (Nardini et al, in press; Tranter et al 2006) we had no specific predictions how individuals with WS would behave in the task. To our knowledge, this is the first report of spatial deficits within a large-scale task involving egocentric movement through the search space, and the results suggest that individuals with WS have difficulties with spatial processing within different frames of reference and at a variety of scales.

The search behaviour demonstrated by the WS participants here is strikingly similar to that recently reported by Montfoort and colleagues (2007). These authors investigated

visual search behaviour in individuals with WS, and found that participants demonstrated particularly inefficient profiles, with longer search times, increased fixation durations, and many more erroneous revisits to items they had already inspected. Since it has been argued that the visual-search task represents a good model for more general foraging behaviour (Klein and MacInnes 1999; Wolfe 1994) one might predict that the visual-search deficits observed in WS would also extend to a large-scale search (or 'foraging') task. The present findings could be seen as support for the hypothesis that inefficient search extends to a large-scale egocentric task, although the tasks rely on highly different representations of space and may be subject to different functional mechanisms (Gilchrist et al 2001; Smith et al 2005, 2008). Montfoort et al (2007) posited that one possible explanation for inefficient visual-search behaviour could be impaired visuomotor control, with participants also fixating locations where there was no item. However, the similarity between the fixation errors observed in their study and the present experiment suggests that a higher-level impairment contributes to the inefficient search of space, in both small- and large-scale contexts.

It is possible that a deficit of visuospatial working memory could contribute to revisit behaviour. As evidenced by scores on the Corsi block tapping task (see table 1), both individuals with WS had smaller spatial memory spans than the PD individuals, and this might have resulted in reduced memory for locations visited on their route through the array. Smith et al (2005) found that Corsi span in typically developing children was strongly related to their search efficiency, supporting the idea that the prevention of revisits in this task relies heavily on visuospatial working memory. Interestingly, revisit behaviour was not related to display size in the present experiment. Whilst WS1 made most revisits when there were 20 locations in the array, WS2 made the most when there were only 5. This suggests that inefficiency is not necessarily a function of load (ie poor memory is not associated with a greater number of locations to store). Another possibility is not that participants with WS had difficulty remembering where they had visited, but that they did not plan their route through the display as efficiently as other participants. Since performance on the Corsi block test also relies on executive functions (eg Vandierendonck et al 2004), a low score could reflect difficulties with inhibition or planning abilities as much as visuospatial short-term memory. A recent report by Porter et al (2007) associates hypersociability in WS to frontal-lobe impairment, especially in the inhibition of responses. This approach could account for the present findings, in that participants with WS may have had more difficulty inhibiting erroneous revisits (cf Smith et al 2005). Parietal patients have been shown to have difficulty remembering previously searched locations (Husain et al 2001), and Montfoort et al (2007) cite this and other evidence (eg Atkinson et al 2003) as argument for a parietal basis to WS spatial impairment. We, however, do not think it is entirely sufficient to characterise WS in the same way that one would a patient with a cerebro-vascular accident. Whilst patient neuropsychology is a very instructive methodology for elucidating the exact nature of cognitive impairments, it is primarily undertaken with a damaged cognitive system. In comparison, developmental neuropsychology must take into account that the system has emerged in a qualitatively different manner. Individuals with disorders such as WS, autism spectrum disorder, and Down syndrome have developed atypically from birth and care is therefore needed when associating their cognitive profiles with those of neurological patients (for discussion see Findlay and Gilchrist 2003, page 163; Karmiloff-Smith 1998, 2006; Karmiloff-Smith et al 2003b; Meyer-Lindenberg et al 2006).

The present study represents the preliminary stage of a larger programme of research into large-scale spatial behaviour in WS. This bigger study examines the associations between large-scale and smaller-scale (eg peripersonal) spatial skills, along with performance on tests of verbal, intellectual, and executive function. We also aim

to more closely ally the study of large-scale search in humans with animal models of foraging and navigation. This is especially important in the present study, as claims about the importance of LIMK1 to spatial processing have in part been derived from rodent data. The task reported here was not designed to exactly replicate the Morris maze, and therefore could be seen to differ from the task demands of a place-learning study (such as that of Meng et al 2002). However, to perform the task efficiently, participants must represent the position of their body within large-scale space, update that representation with their movement, and use this information to code where they have previously been (eg Gopal et al 1989). As such, the task tapped cognitive processes that are closer to those used in animal models of spatial function. We argue that this is an important consideration when attempting to compare between species (Karmiloff-Smith 2006). Furthermore, a full characterisation of spatial abilities in typical and atypical human development, as well as neurological patients, must include measures of large-scale egocentric spatial cognition. In particular, we highlight the importance of testing individuals on a comprehensive range of tasks at different spatial scales before making firm links between genotype and cognitive phenotype.

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