Focus Article

Space and language in Williams syndrome: insights from typical development

Barbara Landau* and Katrina Ferrara

One of the holy grails of cognitive science is to understand the causal chain that links genes and cognition. Genetic syndromes accompanied by cognitive effects offer natural experiments that can uniquely inform our understanding of this chain. In this article, we discuss the case of Williams syndrome (WS), which is characterized by a set of missing genes on chromosome 7q11.23, and presents with a unique cognitive profile that includes severe spatial impairment along with strikingly fluent and well-structured language. An early inference from this profile was the idea that a small group of genes could directly target one cognitive system while leaving others unaffected. Recent evidence shows that this inference fails. First, the profile within the spatial domain is varied, with relative strength in some aspects of spatial representation but severe impairment in others. Second, some aspects of language may fail to develop fully, raising the question of how to compare the resilience and fragility of the two key cognitive domains in this syndrome. Third, much research on the profile fails to place findings in the context of typical developmental trajectories. We explore these points and propose a new hypothesis that explains the unusual WS cognitive profile by considering normal mechanisms of cognitive development that undergo change on an extremely prolonged timetable. This hypothesis places the elements of the WS cognitive profile in a new light, refocuses the discussion of the gene–cognition causal chain for WS and other disorders, and more generally, underlines the importance of understanding cognitive structure in both typical and atypical development. © 2013 John Wiley & Sons, Ltd.

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INTRODUCTION

One of the holy grails of cognitive science is to understand the causal chain linking genes to cognition. Although studies of typically developing individuals surely provide a valuable contribution, genetic syndromes that are accompanied by cognitive effects offer natural experiments that can uniquely inform our understanding. Examples range from studies of language deficits in people with FOXP2 mutations,[1–3] to studies of mathematical disabilities in Turner syndrome,[4,5] and learning deficits in people with Down syndrome.[6–8] In this article, we discuss the case of Williams syndrome (WS), which appears to offer particularly interesting evidence regarding the causal chain between genes and cognition. WS is characterized by a well-defined set of approximately 25 genes missing on chromosome 7q11.23.[9] It is accompanied by a unique cognitive profile that includes severe impairment in a range of spatial functions coupled with strikingly fluent and well-structured language, first reported in the cognitive science literature by Bellugi and colleagues.[10] The early inference from this cognitive profile was that the missing genes specifically targeted spatial cognition, while leaving language unaffected—an inference

*Correspondence to: landau@cogsci.jhu.edu

Department of Cognitive Science, Johns Hopkins University, Baltimore, MD, USA

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consistent with a relatively simple view of the causal chain in which a small group of genes directly targets a specific cognitive system.

This inference is now known to fail for a number of reasons. First, there is now general recognition that genetic variation is likely to map quite complexly onto cognitive outcomes. One cautionary tale is the FOXP2 deficit, which is linked to language disorders and was originally called 'the grammar gene'.[2,11,12] We now know that this genetic change causes a range of deficits in humans beyond language, and that the deficit profile may be rooted in complex motor control rather than language *per se*.[13] Second, recent findings stress the powerful role of epigenetics, showing that the genome interacts with the environment over time, thus changing over the lifetime and thereby ruling out simplistic causal chains.[14] A compelling example of this is the recent finding that individuals with high IQ show later increases in IQ heritability than low IQ individuals, suggesting the former may have an extended sensitive period that can be affected by the environment.[15]

For our purposes in this review, one of the central reasons for the failure of the causal chain inference is that the initial characterization of the WS spatial deficit was quite limited in scope, as well as devoid of the rich theoretical framework available from research on spatial representation in humans and other species. Specifically, early research on WS focused on a small set of visual–spatial construction tasks that require copying an existing configuration by putting together blocks or by drawing. Numerous studies have shown that children and adults with WS do indeed have severe impairments in such tasks, regularly performing below the 20th percentile for their age[16] and often showing equivalence to typically developing 4–5-year olds.[17] However, such construction tasks are highly complex, drawing on many basic aspects of cognition including representation of individual elements of the design, the spatial relationships among those elements, and the more global executive functions that guide the iterative processes required to construct a copy.[18] Moreover, use of construction tasks underestimates the distinct internal architecture and structure of the multiple systems underlying spatial representation (see Ref 19). Rectifying this approach requires that we look as broadly as possible at the WS profile within the various systems of spatial representation. This will reveal whether deficits persist equally across all areas of spatial representation or, alternatively, are better characterized by uneven effects—a portrait of peaks and valleys within the broad domain of space. Searching for the details of the spatial profile is especially important because it is well known that different spatial systems (e.g., object representation, navigation, visual–manual action) are supported by different brain systems, which could in principle be individually linked to specific sets of genes.[a] Evidence shows that the WS brain has many atypical structural characteristics,[20–22] as well as atypical functional properties in parietal areas and the hippocampus.[23–25] These findings suggest the possibility that there may be uneven impairment across fundamental spatial systems.

An analogous issue exists for the evidence on language. Early studies focused on grammatical judgments of complex structures and strength in vocabulary, with the latter supported by the presence of relatively complex and low-frequency words in production.[10] Over the past 15 years, several investigators have argued that the picture of language as 'spared' is inaccurate, with systematic tests of morphology and syntax revealing distinct areas of weakness[26] and more rigorous testing revealing no clear evidence for low-frequency and unusual vocabulary.[27] The idea that syntax, semantics, and morphology are 'spared' is still quite controversial, a topic to which we return (see Refs 28 and 29 for discussion).

We explore both of these issues next. But before we do, one crucial question arises: What constitutes the appropriate control group for people with WS? Many of the earliest studies by Bellugi and colleagues (e.g., Ref 30) compared performance of people with WS to that of people with Down syndrome. This comparison made sense because both groups are characterized by mild to moderate mental intellectual disability, and hence could be considered equivalent for mental age, leaving spatial ability the variable of interest to be measured. Other studies have sometimes used chronological age matches as controls (including early studies of grammatical judgments, e.g. Ref 10, as well as research on face recognition, e.g. Ref 31). Many studies have also included typically developing children who are matched to WS participants on mental age, most often measured by a standardized test of intelligence such as the Differential Abilities Scale[32] or the KBIT.[33] These methods might appear to provide a way of factoring out 'intellectual disability' by equating on mental age, but this is only if we have confidence that we truly understand what is meant by intellectual disability, or indeed, what exactly is measured by standardized tests of intelligence. We believe that both these assumptions may be challenged.

Some researchers have addressed this problem by matching WS and typically developing individuals on variables that will then allow further, more nuanced comparisons. For example, Mervis and colleagues matched participants on relational vocabulary, and then measured performance on nonspatial relational

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terms compared to spatial terms. It was found that children with WS showed no deficit specific to spatial terms, given their vocabulary level, whereas earlier studies had suggested such a deficit.[34] Thus there are ways to carefully match control groups; but even so, this presumes that one has selected a matching variable that will lead to an informed inference.

An alternative to these matching approaches is to assume that development in people with WS (or for that matter, any unusual population) can best be understood by comparing performance to that of typically developing children of different chronological ages. By examining the normal developmental trajectory for different spatial functions, we can develop a profile against which we can compare the performance and development of people with WS. Examining the trajectories for different spatial functions is important since it is likely that these will vary in the shape of their growth curves (e.g., linear, nonlinear), and progress at different rates. Comparing points of development in WS against full typical developmental curves ensures that we know where people with WS stand relative to typically developing individuals of different ages, who are at different points along the full developmental trajectory for the domains of interest (see Refs 35 and 36).[b] As we will see, examining both space and language against trajectories for normal development reveals a very different way of thinking about the mechanisms underlying the WS cognitive profile.

THE SPATIAL PROFILE

Studies of a broad range of spatial functions have now shown that the WS profile is not correctly characterized as one of severe deficit across all aspects of spatial representation. Rather, the profile for a range of spatial functions appears to align surprisingly well with the profile shown by typically developing young children. For example, studies of orientation discrimination and integration show quite different profiles for people with WS relative to normal adults; but quite similar profiles relative to typically developing children under the age of 6 (see Figure 1).[37] Consider first the normal developmental profile for the following two tasks. *Orientation discrimination*, in which participants are asked to match an oriented Gabor patch to one of several choices, shows a lengthy trajectory of development for typically developing individuals. The thresholds of typical 3–4-year olds are far higher than those of adults and the development of this spatial function changes slowly over time, with 9-year olds approaching the adult level. Adolescents and adults with WS perform at the level of normally developing 3–4-year olds, and are hence functionally immature even in adulthood. In contrast, *orientation integration*, in which people are asked to identify a contour created by oriented elements, shows a rapid developmental trajectory, in which 3- and 4-year olds have already attained thresholds close to those of adults. Adolescents and adults with WS perform like typically developing 3–4-year olds, which is adult-like; hence this function is mature in people with WS by adulthood. Importantly, the profile for WS differs depending on the typical developmental trajectory: Functions that are typically early-emerging reach normal levels of mature functioning in people with WS, but functions that are typically late-emerging do not.

Similar patterns have been uncovered for other spatial functions, including object recognition and visual–manual action, as well as numeric estimation. Children and adolescents with WS (mean age 11 years) recognize briefly presented objects (both full-color and line-drawings) at close to ceiling levels when the objects are presented in canonical orientations (e.g., a ¾ view of a chair), but show quite poor performance when presented with objects in unusual orientations (e.g., a stool from the underside).[38] Typically developing 4-year olds also perform well with objects in canonical orientation but poorly with objects in unusual orientation, with the latter performance at the same levels as the WS group (see Figure 2, see also Ref 17).

Levels of performance for objects shown in unusual orientations do not reach adult proficiency in typically developing children until adolescence, suggesting that object recognition for canonical versus unusual views proceed on quite different developmental trajectories. The WS pattern of performance in early adolescence suggests that canonical view recognition has reached the normal mature level but that unusual view recognition has been stalled at the early functional level of typically developing 4–6-year olds. The same pattern holds in the area of visual–manual action. When children and adults with WS are asked to 'post' a dollar bill into an oriented slot, their performance is no different from typically developing 3–4-year olds, and worse than mental age-matched controls[39] (see Figure 3).

Recent work in our lab has also focused on the approximate number system (ANS) in people with WS. Over the course of typical development, the resolution of the ANS (as specified by the Weber fraction) improves between ages 3 and 6, and becomes adult-like even later in development.[40,41] When asked to compare the numerosities of two displays of dots which are presented briefly to prevent explicit counting, adolescents and adults with WS demonstrate a profile quite similar to that of typically developing

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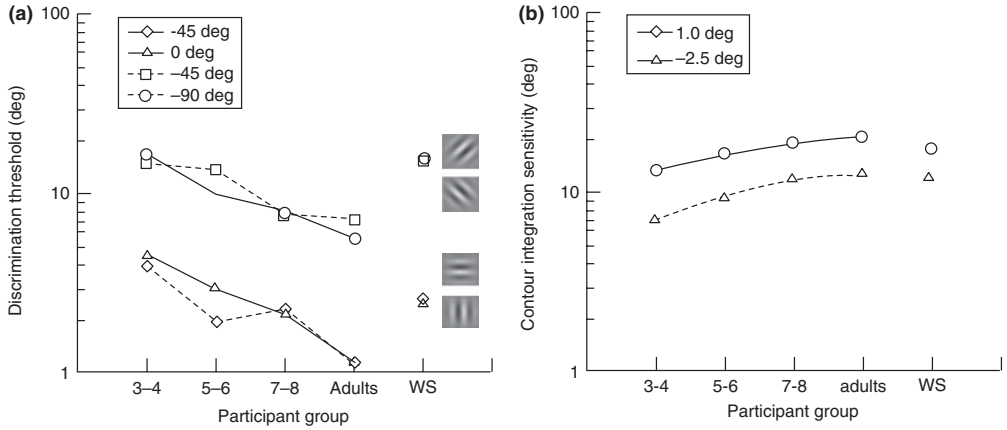

FIGURE 1 | (a) Orientation discrimination threshold (geometric mean) as a function of participant group. Discrimination becomes adult-like after the age of 6 years in typically developing children, and is at the level of normal 3–4-year olds in adolescents and adults with WS. This suggests that orientation discrimination typically develops over a lengthy trajectory, and is functionally immature in adolescents and adults with WS. (b) Orientation integration (contour detection) sensitivity as a function of participant group. Integration sensitivity becomes adult-like after the age of 4 years in typically developing children, and is at the level of normal adults in adolescents and adults with WS. This suggests that orientation integration in WS is functionally mature. This pattern is consistent with the idea that spatial functions that typically develop early (such as orientation integration) reach maturity in people with WS, but functions that typically develop over a lengthy trajectory (such as orientation discrimination) do not reach maturity in people with WS, even in adulthood. (Reprinted with permission from Ref 37. Copyright 2008 Elsevier Inc.)

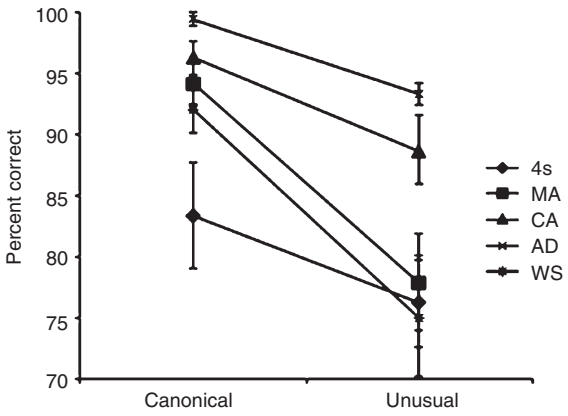

FIGURE 2 | Mean percent correct as a function of viewpoint presentation (canonical versus unusual). Separate lines correspond to different groups [4's: typically developing 4-year olds; MA: mental age matches to WS participants (mean age = 5;8); CA: chronological age matches to WS participants (mean age = 11;11); AD: normal adults; WS: Williams Syndrome (mean age = 11;0).] Children with WS performed as well as CA matches for canonical presentation, but only as well as typically developing 4-year olds and MA matches for unusual presentation. Overall, unusual views have a more protracted developmental time course than canonical views in both typically developing children and people with WS. (Reprinted with permission from Ref 17. Copyright 2012 Oxford University Press)

4-year-old children,[42] consistent with related findings from Ansari et al.,[43] O'Hearn and Landau,[44] and Opfer and Martens.[45]

Thus, across very different spatial functions, people with WS appear to reach the level of performance shown by a typically developing 4–6-year old. Spatial functions that typically mature early (e.g., by age 4 or 5) are also observed to reach normal adult levels among people with WS, but those that typically show lengthier developmental trajectories appear to be arrested at an early functional level, with little change thereafter.

Is this profile true for all spatial functions? One area of current controversy is navigation, a complex system that is supported by a number of different mechanisms engaging the hippocampus and a network of other regions. For example, the parahippocampal place area (PPA) is sensitive to geometric properties of scenes such as perspective, volume, and open/closed spatial layout.[46,47] The retrosplenial cortex (RSC) is also involved in scene perception but is especially sensitive to scene and landmark familiarity.[48] Recognition of landmarks and scenes is crucial for navigation, but there are different ways that this information can be used during navigation. Recent studies show that the hippocampus and the dorsal striatum use different kinds of information and support different kinds of learning. In humans, the hippocampus is implicated in incidental learning of places as defined by environmental geometric structure, especially boundaries[49]—known to be crucial for reorientation in animals.[50,51] In contrast, the dorsal striatum supports the learning of places relative to landmark locations, which may support navigation through associative learning mechanisms.[49] Adult human imaging evidence from

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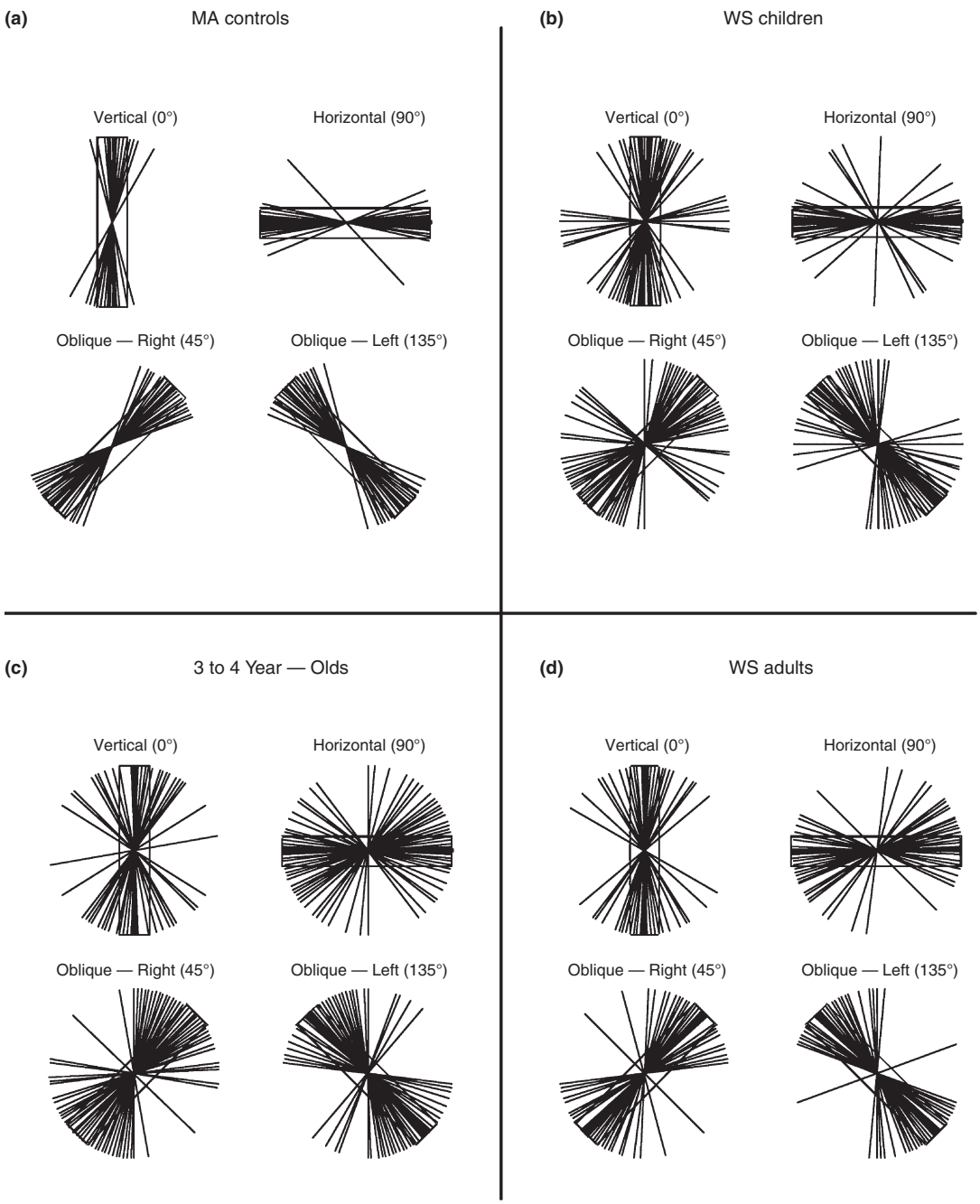

FIGURE 3 | Radial plots of individual responses for each target orientation in the Action task. Individual responses are denoted by nonbolded lines and the rectangular box indicates the 10° allowance around the target slot. [MA controls ranged in age from 4;7 to 9;6 (mean = 6;3), WS children ranged in age from 8;3 to 16;2 (mean = 12;0); WS adults ranged in age from 19;3 to 32;3 (mean = 23;9)]. WS children and adults both showed the same profile as typically developing 3–4-year olds, which was more errorful than the MA controls. (Reprinted with permission from Ref 39. Copyright 2008 John Wiley and Sons, and Ref 17. Copyright 2012 Oxford University Press).

virtual reality tasks further suggests that linking geometric structure and landmarks engage both the hippocampus and PPA.[52]

Given documented abnormalities in both the parietal and hippocampal areas in people with WS,[24,25] one might predict especially severe impairment in navigational abilities. Indeed, several studies have suggested that there may be deficits in aspects of navigation among people with WS. Farran et al.[53] found poorer performance than

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chronological age-matched controls on a virtual reality route learning task, and Nardini et al.[54] found that even adults with WS had great difficulty locating an object on an array that had been rotated, which changed the spatial relationships between all objects and available landmarks. Strikingly, however, these studies also demonstrate that people with WS show strong competence in several core aspects of navigation that emerge early during typical development. For example, Farran's study[53] showed that WS participants could learn routes to criterion, even though it took more trials than controls, and Nardini et al.[54] found that participants were able to accurately locate objects in the array after they themselves had moved, showing that they could update their own position after movement. Moreover, like typically developing 3- and 4-year olds, people with WS performed best when their position with respect to the experimental array remained stable (allowing them to rely on multiple reference frames), or when they themselves moved (allowing them to use a room-based, but not an egocentric frame of reference). In both Farran's and Nardini's studies, recognition and use of landmarks was crucial to success in the task. Thus the ability to learn routes, update one's own position over movement, and use landmarks are all functional parts of the navigation system in people with WS.

In contrast, a recent study of reorientation, in which people are required to locate an object after being disoriented, suggested that one foundational aspect of spatial representation may be especially compromised in people with WS. Cheng and Gallistel[55,56] were the first to identify the crucial role played by sensitivity to the geometry of layouts in the ability of many species—including human toddlers, children, and adults—to reorient successfully (for review, see Ref 57). Given this widespread and apparently universal pattern, Lakusta et al.[58] tested whether people with WS could also use geometry to reorient themselves after they became disoriented. Following the design and procedures of Hermer and Spelke,[59] and using an all-black rectangular room, Lakusta et al.[58] found that, of 19 people with WS (mean age 17 years, range 9;9–27;9), only 5 used geometry. In contexts where a landmark could also be used to find the hidden object (i.e., addition of a single blue wall), 16 of the 19 people used the landmark. Figure 4 below illustrates these results, along with a control condition, which demonstrated that people with WS are unimpaired in locating the same targets when they have not been disoriented.

Lakusta et al.'s findings suggest that although people with WS are unable to use strictly geometric information about layout to inform their search, they can often use a clear landmark to do so. This pattern differs qualitatively from any pattern previously observed in typical human development or among typical adults.

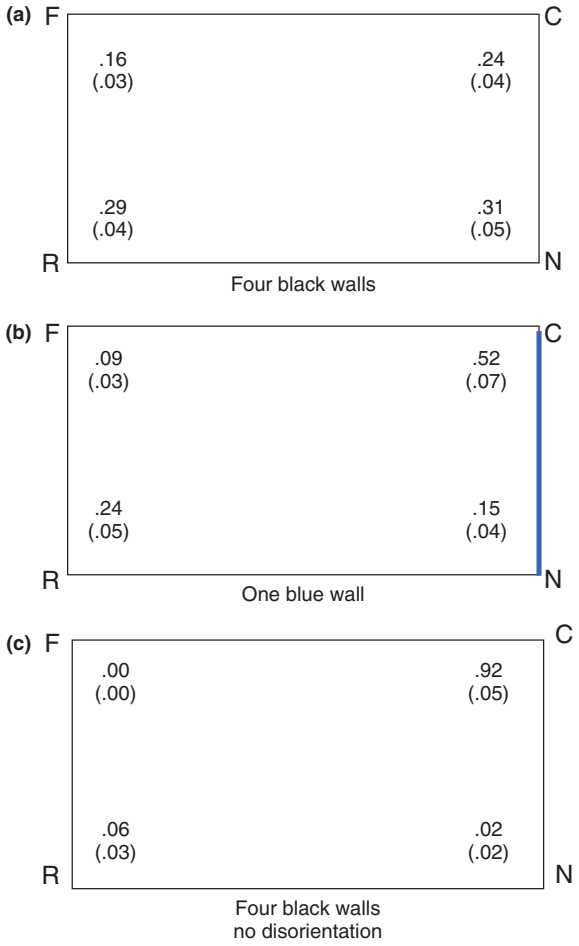

FIGURE 4 | Results from Lakusta et al.[58] Values indicate the average proportion of search (and SEs) at each corner (C = correct, R = rotationally equivalent, N = near, and F = far) for the WS participants in Experiment 1 (a, four black walls; b, one blue wall) and Experiment 2 (c, four black walls, no disorientation). In a, searches were evenly distributed among the corners of the room with four black walls, showing lack of sensitivity to the geometric layout. In b, the proportion of search at the correct corner (.52) is higher than that at the other three corners. This shows that participants often used the landmark cue of the blue wall to help them locate the hidden target. In c, participants were highly accurate when they were not disoriented. (Reprinted with permission from Ref 58. Copyright 2010 National Academy of Sciences, and Ref 17. Copyright 2012 Oxford University Press).

These results suggest that reorientation in people with WS could be a case of catastrophic breakdown, with failure to use the geometry of layouts among the majority of the participants. However, a recent replication and extension suggests that this conclusion

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is too strong.[60] By modifying the layout slightly to enhance the salience of the room's corners and object's hiding locations, we found that of 16 WS children and adults (ages 5;8–32;8), 14 used geometry; most also used landmarks. This suggests that people with WS do show sensitivity to geometric information during reorientation, but that they may require especially salient presentation of the information for maximal use. Of additional interest was the pattern shown by some of the youngest WS children in the sample, who used geometry but ignored the landmark—the same error pattern often attributed to young typically developing children (18 months–4 years).[59] The overall findings suggest that geometric sensitivity is available to at least some people with WS from early on in development, and that full integration of geometry and landmarks may await adolescence. This would be consistent with the many other results we have described that illustrate slow development but ultimate mastery for those functions typically acquired early in typical development.

THE LANGUAGE PROFILE

Perhaps the most hotly debated aspect of the WS cognitive profile concerns knowledge of language. Early studies showed that adolescents with WS could judge the grammaticality of complex sentences.[10] In the context of moderate intellectual disability and severe spatial deficits, this led scientists to propose that WS exemplified a case of modularity, in which missing genes targeted specific cognitive systems, with language 'spared'—that is, unaffected by the genetic deletion. Since that time, however, the claim of sparing has been challenged, and along with this came a challenge to the idea that WS exemplifies evidence for cognitive modularity. Two key arguments have been made against the idea of 'spared' language in people with WS. First, some have demonstrated that the overall language levels attained by people with WS are not equivalent to chronological age-mates, arguing against the idea of complete sparing (e.g., Ref 26). Indeed, studies have shown that people with WS often perform more like much younger typically developing children who have been matched for mental age.[61] A second argument concerns the internal structure of language. Here, arguments have been made that the language of people with WS is structurally different from that of typically developing children, suggesting that an abnormal language system has been constructed.[62,63] This argument is quite controversial, however, as many others have argued that the system constructed by people with WS is no different in structure from that of unaffected individuals, including syntax, semantics, and morphology.[28,64–68]

There are several important nuances that are often missed in discussions of WS language. First, the idea of 'sparing' requires refinement. Is the target language system one characterized by *knowledge* of language, or alternatively, by *implementation* of language structures in various task contexts? Several careful studies have revealed that, if one tests for the presence of linguistic knowledge, people with WS are found to have structural knowledge of many core aspects of syntax, semantics, and morphology. For example, Zukowski[68] studied production of relative clause structures by children and adolescents with WS. As she notes, studies of relative clause comprehension often use the TROG,[69] a test in which people hear sentences of varying complexity and are asked to indicate which of several pictures matches the meaning of the sentence. On this test, people with WS perform roughly at the same level as much younger typically developing mental age-matched children. Some have offered these results as evidence that WS syntax is not 'intact.'[26,27] Zukowski reasoned that people with WS could possess knowledge of relative clauses structures but have difficulty processing them, due to impairments in ancillary processes such as working memory. She devised a task that provided felicitous conditions for people to produce complex relative clause structures, and found that almost every participant with WS successfully produced both object and subject-relative clause structures in sentences that were appropriate for the context. This provides striking evidence that people with WS possess knowledge of relative clause structures, even if they have difficulty processing them in some contexts.

It is notable that this knowledge of syntax is also evident in typically developing 5–6-year olds. This is important because it shows both that complex linguistic structures are part of the knowledge system acquired by people with WS, and that such complex knowledge is also acquired by typically developing children relatively early in life. The pattern of WS mastery of knowledge that is typically acquired early in life parallels what we have argued as the mode for spatial representation. It once again suggests that people with WS may undergo quite slow development, and that the knowledge that is acquired is *typical for developmental level*.

The larger point made by Zukowski's study is that we must be careful to examine in detail the linguistic structures that are acquired by people with WS, and we must be wary of drawing conclusions solely based on complex tasks (such as the TROG) that engage mechanisms and representations not directly

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relevant to the question of linguistic knowledge (e.g., matching to a picture, which itself requires interpretation). Further studies of complex syntax and semantics take this point one step further. Musolino et al.[28,64] examined the capacity of children and adolescents with WS to represent complex interactions between syntax and semantics, using well-known interactions between negation and disjunction as they are modulated by syntactic structure (specifically, hierarchical structure and c-command). Musolino et al. found that people with WS could make subtle distinctions in meaning between such minimally contrasting sentences as 'The cat who meows won't get a fish or milk' (i.e., the cat gets neither) versus 'The cat who doesn't meow will get a fish or milk' (i.e., the cat gets either). Using a truth-value judgment task, Musolino et al. found that WS individuals and typically developing children demonstrated knowledge of these complex structures, performing well above chance when interpreting these sentences. Typically developing children also perform above chance from about age 5. In quantitative terms, the WS group performed worse overall than typically developing 5–7-year olds, and better than 4-year olds, fitting in between these two groups. These findings are again consistent with the hypothesis that people with WS—and typically developing 5-year olds—develop linguistic knowledge that is rich and complex, allowing them to perform well above chance in interpreting complex sentences. This could occur if people with WS developed on an extremely slow timetable, reaching the level of a typically developing 5- or 6-year old by adolescence.

Language acquisition in people with WS may not only undergo slow development, but there may also be arrest during adolescence. Many of the empirical results we have cited (and reviewed in Ref 17) show that the WS adolescent performs on roughly the same level as a typically developing 5-year old. Developmental arrest would imply no further growth beyond this point. The arrest hypothesis suggests that structures typically acquired late in development may never be acquired by people with WS—or indeed, might be acquired in a way that fits 'late learning' by normal individuals. Supporting evidence for this hypothesis includes studies of late-developing linguistic knowledge such as raising (i.e., moving subjects or objects into prominent sentential position), as well as certain passives.[70] These are not completely mastered by many people with WS, nor are relatively abstract uses of spatial prepositions, which are typically acquired after age 6.[17]

One final puzzle concerns the growth of 'open class' vocabulary, which may show a different trajectory from other aspects of language acquisition. This part of vocabulary (primarily nouns and verbs) admits new members over time through technological and cultural change (e.g., *google*, *tivo*) and typically continues to grow throughout one's lifetime. Most standardized 'verbal' measures used to test people with WS tap knowledge of open class words; for example, the KBIT[33] includes test items such as *clock* at early levels, *emblem* at more advanced levels, and *convivial* and *mollify* at the most advanced level. Measures of the growth of this vocabulary have indicated relative strength among people with WS and this may be because they continue to acquire this class of words throughout their lifetime.

In contrast, many members of the so-called 'closed class' vocabulary are typically fully mastered early in life, by the age of about 5 or 6. This class includes determiners, quantifiers, and prepositions. Each form a small 'closed' set that does not admit new members over time, and members are often considered to be part of the grammatical and morphological systems of a language. Acquisition of many closed class items appears to be subject to a sensitive period for learning; for example, some uses of determiners and spatial prepositions are never mastered fully by people who learn English as a second language after the age of about 8.[71,72] This raises the intriguing question of whether people with WS—who might be learning over a highly protracted timeline—might also struggle with some closed class items.

Two studies indicate that adolescents with WS still struggle with the morphology of determiners and adjectives, with one study suggesting that they show error patterns virtually identical to those of much younger children.[26,66] The evidence on spatial prepositions also suggests some deficits among adolescents and adults with WS. For example, directional uses of *right* and *left* show poor performance among WS adolescents and adults, who make errors similar to those of normally developing 5–6-year olds.[65] Moreover, spatial preposition uses that are difficult for second language-learners (e.g., *bird in a tree*, *dent in a can*)[72] are not fully acquired by adolescents and adults with WS, who only reach a level commensurate with typically developing 4–6-year olds.[17,34,65] These difficulties with spatial prepositions may be specific to the spatial content, but we think the facts fit with the possibility that people with WS struggle to reach full maturity on aspects of language that are typically acquired past the age of 6. This view would predict difficulties with other parts of the closed-class vocabulary that might, too, undergo prolonged normal development—for example, constructions involving quantificational terms such as *each* and *every*.[73]

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In summary, there may be a stark contrast between the growth of the open class vocabulary in people with WS (which might continue to grow throughout the lifetime), and selective limits on the acquisition of closed class items, with only those fully acquired early in typical development reaching full maturity. These two parts of the vocabulary may be subject to different learning mechanisms and sensitive periods for acquisition, leading to different acquisition profiles within and across groups.

CONCLUSION: A NEW HYPOTHESIS ABOUT THE WS COGNITIVE PROFILE

The hypothesis of slow development and arrest during adolescence fits many empirical facts about both the spatial and linguistic profile of people with WS. The hypothesis is rooted in the fact that different systems of spatial representation and different subsystems of language appear to undergo different developmental trajectories over the life span of the normal individual. Some spatial functions (including recognition of objects under canonical viewpoints, integration of oriented elements to produce the perception of more global forms, reorientation using geometric properties of layouts) undergo rapid and early development in normal children. Similarly, some aspects of language (including growth of the open class vocabulary and representation of hierarchical structure in sentences) also emerge by the time typically developing children are around 5 years of age. Those aspects of both space and language that are acquired early in life are also present in people with WS, even if they are acquired by a later chronological age. In contrast, the many aspects of space and language that normally emerge later in development (including some aspects of visual–manual action, representation of the more abstract meanings for spatial prepositions, some aspects of passive constructions) may never develop to the level of typical adults in people with WS.

A graphic representation of this hypothesis appears in Figure 5. Two different functions are shown, one that represents the development of typically early-emerging spatial and linguistic abilities (blue), and one that represents the maturation of spatial and linguistic abilities that typically progress on a more prolonged time scale (red). Along the *x*-axis, we show the ages at which both typically-developing children and WS individuals attain mastery of these classes of early- and late-emerging abilities. For typically-developing children, we see that some aspects of space and/or language are close to maturity by ages 4–5, whereas other aspects do not reach maturity until much later in life. The ages of the WS population along the *x*-axis (more than double those given for the case of typically developing children) reflect our hypothesis that the development of both spatial and linguistic functions is characterized by significantly protracted trajectories within this population. During adolescence, we hypothesize that many people with WS undergo developmental arrest (indicated by the dashed vertical line in the figure). This means that once they have reached the developmental point of a typically developing 4–5-year old, they remain at this functional level.

By this hypothesis of slow development followed by arrest, the root cause for the oft-cited unusual cognitive profile for people with WS—strong language and severely impaired spatial functions—is the following: if one undergoes extremely slow (but otherwise normal) development, followed by overall plateauing in adolescence, this would result in cognitive representations for both space and language that are quantitatively and qualitatively normal *for a much earlier developmental point*. This hypothesis differs considerably from previous hypotheses proposed to explain the WS cognitive profile, including the hypothesis of dorsal stream disorder,[65,74,75] global processing deficit,[76] or a disorder resulting in a 'deviant' cognitive architecture, that is, one that is qualitatively different from any observed in typical development.[77,78]

Our hypothesis of slow development followed by arrest is currently an inference based on a large set of studies in our lab and those of others that have been carried out cross-sectionally, that is, testing individuals with WS at different ages. Further tests of the hypothesis will require establishing developmental trajectories for different spatial and language functions using longitudinal studies of individuals with WS, and comparing these trajectories with those of typically developing individuals. Of special interest will be spatial and language abilities that are typically acquired relatively late in development; our hypothesis predicts that these abilities will be severely impaired, whereas abilities acquired early in development will emerge, albeit at a later age than in typical development. Importantly, the slow development plus arrest hypothesis may be pertinent to explaining other developmental disorders that result in unusual cognitive profiles. For example, recent theories of the intellectual disabilities of people with Down syndrome have characterized the syndrome as affecting late-developing neural structures, including the hippocampus and prefrontal cortex,[79] or resulting from poor communication between late-developing regions.[80] Other studies suggest that aspects of memory for faces that typically continue to develop

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FIGURE 5 | Model of hypothesized mechanisms underlying the WS spatial and linguistic profile. The model shows a hypothetical developmental curve for early emerging spatial and language functions (blue), contrasted with those that are late emerging (red). People with WS are hypothesized to undergo very slow development for both spatial and language functions, followed by arrest, resulting in a mature cognitive profile that resembles that of a typically developing 4–6 year-old (and indicated by the vertical dashed line; see text for discussion). (see text for discussion). (Reprinted with permission from Ref 17. Copyright 2012 Oxford University Press.

through adolescence are halted in autism.[81] Our focus on developmental trajectories for space and language might also be useful in understanding individual differences in typical development, especially given the recent suggestion that high-IQ individuals may experience a prolonged sensitive period for cognitive development, providing them with greater opportunities to learn than low-IQ individuals.[15]

There are rich prospects for future research on the cognitive profile of individuals with WS. These include directly testing the hypothesis of slow development followed by arrest using well-articulated theories of spatial and linguistic structure, carrying out studies focusing on human cases of small deletions within the WS region, using mouse knock-out models to probe the relationships between particular genes and cognitive outcomes,[82,83] examining in detail the connection between fragility in the navigation system and possible correlates in well-defined regions of neural activity, and building on the insights of epigenetics to take a serious look at variation in the environments of children and adults with WS.[84] Evidence inconsistent with our hypothesis will, of course, also have to be explained in a theoretically rigorous fashion (see Ref 29). More generally, we will achieve the deepest understanding of the gene-brain-cognition relationship if we use theoretically-informed models at each level of understanding.

In conclusion, we should note that our hypothesis captures a wide range of empirical facts about the cognitive profile of individuals with WS, but it does not explain all aspects of this profile. For example, many people with WS learn to carry out moderately complex levels of formal math, performing on average at the third-grade level on a standardized measure, the Test of Early Mathematical Abilities.[44,85] Many people with WS also learn to read, and some show mastery of components that are in line with their chronological age.[86] These facts do not fit with the idea that cognition in people with WS is *solely* characterized by slow development and arrest in adolescence. Clearly, these formal skills have been learned despite the fact that some foundational skills (e.g., orientation discrimination for letters, numerical estimation) remain at levels far below chronological age. The mechanisms by which children and adolescents with WS come to learn higher-level skills such as reading and formal symbolic maths are unknown. But they point to the fact that experience plays a crucial role in shaping the ultimate developmental outcomes for people with WS. Completing the causal chain between genes and cognition in WS will ultimately require understanding the limitations imposed by this genetic deficit, as well as the advances that can be made despite these limits.

NOTES

[a] That is, it is possible that certain genes may target specific cognitive systems within the broad range of abilities that fall under the umbrella of spatial cognition. Future research is needed to determine whether particular genes within the deletion range

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of WS are uniquely linked to the particular aspects of spatial functioning that are severely impaired within the population.

[b] In practice, inferences about the shapes of different developmental trajectories have largely been based on the results of cross-sectional research. There are few studies that establish developmental trajectories using a longitudinal approach, either for individuals with WS (but see Ref 35) or typically developing children (see Ref 36). Longitudinal studies will be critical to establishing the shapes of spatial–cognitive growth curves and their variation over individuals.

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