Williams syndrome and its cognitive profile: the importance of eye movements

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Abstract

People with Williams syndrome (WS), a rare neurodevelopmental disorder which is caused by a deletion on the long arm of chromosome 7, often show an uneven cognitive profile with participants performing better on language and face recognition tasks, in contrast to visuo-spatial and number tasks. Recent studies have shown that this specific cognitive profile in WS is a result of atypical developmental processes that interact with and affect brain development from infancy onwards. Using examples from language, face processing, number, and visuo-spatial studies, this review will evaluate current evidence from eyetracking and developmental studies and argue that domain general processes, such as the ability to plan or execute saccades, influence the development of these domain specific outcomes. Although more research on eye movements in WS is required, the importance of eye movements for cognitive development suggests a possible intervention pathway to improve cognitive abilities in this population.

Keywords

Williams syndrome, eye movements, face processing, language, number, visuo-spatial abilities

Introduction

Williams syndrome (WS) is a rare neurodevelopmental disorder which results in a specific clinical, behavioral, and cognitive profile. This uneven cognitive profile has been of interest in order to unravel links between genetic make-up, the brain, and behavioral outcomes (eg [1,2,3,4,5]). Studies have often claimed that WS provides evidence for a modular cognitive theory in which certain abilities can be spared or impaired and that these impairments can be directly linked to the WS genotype. [6,7] . Yet, as argued elsewhere, modules observed in adults emerge as a result of development and domain specific behavioral outcomes are supported by domain general cognitive processes from infancy onwards. [8,9] In order to study the connections between genes, brain, and behavioral outcomes, it is therefore important to understand how the cognitive processes in WS differ from those in typically developing (TD) populations, and how they develop over time. [8,9,10,11] In addition, a better understanding of what domain general abilities relate to performance in WS, including those that can explain areas of cognitive strength as well as a weakness, can further aid the development of ecologically valid training and intervention programs. Using evidence from two cognitive areas considered to be a strength: face and language processing, and two areas of weakness: visuo-spatial and number abilities, this review will evaluate how atypical looking behavior observed in eyetracking as well as developmental studies in WS can explain some of the domain specific outcomes in adulthood. Eyetracking studies were identified through searches (through to January 2015) in PubMed, Web of Science, and Google Scholar using “Williams syndrome” and “eyetracking” as keywords (for a similar methodology see [12] applied to research on autism).

Williams syndrome: an uneven cognitive profile

Williams syndrome (WS) is a relatively rare neurodevelopmental disorder with a prevalence between 1 in 20 000 and 1 in 7500 live births. [13,14] It is caused by a micro-deletion on the long arm of chromosome 7, affecting approximately 26-28 genes. [15,16] WS is diagnosed phenotypically based on clinical features as well as genetically using the gold standard fluorescent in situ hybridization (FISH) testing to confirm the deletion of genes on chromosome 7.

WS is a multi-system disorder with a specific clinical, behavioral, and cognitive profile. [17,18] During the last decade, WS has been of interest to researchers because of its uneven cognitive profile. Despite average overall IQ scores of 55, which indicates a mild- to moderate intellectual disability, face-processing and language abilities in WS are generally better compared to drawing, visuo-spatial, memory, and number processing. [7,19,20] Because of the apparent discrepancy between the cognitive domains, especially between language abilities and spatial cognitive deficits, WS has been taken as evidence in favor of a modular theory in which specific, independent, and innate modules can be spared or impaired. [7,19,20,21] However, this discrepancy between the strengths and weaknesses in WS only emerges over time with verbal abilities developing at a faster rate than non-verbal abilities. [22] In addition, considerable heterogeneity has been reported when it comes to discrepancies within the WS profile with some participants scoring very low on language measures while others score within the normal range on visuo-spatial tasks. [23,24] Finally, studies that have examined how abilities change throughout the lifespan have demonstrated that behavioral outcomes, even those in which WS are proficient, rely on different underlying cognitive processes and thus, performance in WS is often atypical rather than just impaired (see [25,26,27] for examples). For example, although participants with WS perform within the normal range on the Benton Face Recognition task, a task in which participants need to match unfamiliar faces, [25,28,29] in depth studies looking at the underlying cognitive processes of performance revealed that people with WS tend to look more at individual features of faces compared to controls who are more likely to process faces holistically. This suggests that individuals with WS might have weak central coherence and thus process faces atypically. [25,30]

Language is another area in which people with WS perform comparatively well, in that the speech of older individuals with WS is better than one would expect for their overall cognitive abilities with good auditory memory and vocabulary skills while syntactic, morphological and pragmatic abilities are lower than predicted by CA. [7,31] However, a review of language abilities in WS has shown little evidence of language abilities being better than non-verbal abilities. [32] In addition, studies in infants with WS have found that the onset of language is not only delayed [27,33] but that the performance on language tasks results from different underlying processes with language development following atypical pathways.[27] For example, in contrast to typically developing (TD) infants, those with WS do not use referential pointing before they start using referential language. Yet, this lack of referential pointing could not be attributed to delayed motor skills in WS. [27,34] In addition, children with WS showed a reduced ability to follow the experimenter's point. It has been argued that this impairment in pointing comprehension might affect their ability to learn vocabulary through parental pointing. [35]

Visuo-spatial cognition, often assessed by drawing tasks, block building or pattern construction tasks, has been found to be an extreme weakness in WS as performance is much lower with respect to age norms and overall IQ (for a review see [36]) and develops at a much slower rate than in TD controls[22] with performance scores on pattern construction tasks often at floor level. [37] There is evidence that even on visuo-spatial tasks where performance seems to be typical and in line with TD participants, participants with WS rely on atypical strategies. For example, visual illusions require participants to integrate a local part with surrounding elements into a coherent image. Behavioral studies have shown that participants with WS are susceptible to visual illusions to a similar extent as TD individuals. [38,39] Yet, Grice and colleagues[40] demonstrated that this performance is supported by atypical neural behaviors. The Kamisza square illusion occurs when four Pacmen discs are correctly aligned so that the contours of a white square are perceived. This illusion is not perceived when the discs are rotated and it has been argued that this illusion depends on low-level visual processes. Participants with WS were able to perceive the contours of the Kanisza square illusion to a similar extent as TD aged-matched controls, which suggests that low-level visual processes that are intact in WS. However, the N1 component is a negative deflection in the ERP waveform at about 145-180 ms post-stimulus that has been shown to be particularly sensitive and reliable measure of processing of contour illusions. Although the N1 response itself was typical in WS, differences in amplitude of the N1 to the different stimuli was abnormal compared to controls. This suggests that the ability to perceive illusions is supported by atypical cognitive processes in WS.

Finally, studies that have investigated number abilities in children and adults with WS have revealed that arithmetic skills are severely impaired even in adulthood. [41,42] Although children with WS are proficient at counting sequences[43], they are impaired in their understanding of the meaning of counting or the cardinality principle. [44] Research in TD populations has provided evidence that number abilities rely upon two different systems: one for precise and accurate number abilities, such as counting, which relates to language and memory abilities and a second non-verbal magnitude system that relies upon the ratios presented and relates to people's mental number line. [45] It has been argued that this magnitude system is predictive of mathematical abilities later on in life[46,47] and this system has been found to be impaired in WS. [43,48,49,50] However, mathematical abilities are not only impaired, there is also evidence that they develop atypically: whereas non-verbal spatial abilities predicted the variance in TD controls, performance on counting tasks in the WS group related to their verbal abilities. [44] In addition, the developmental trajectory of the WS group was atypical as estimation abilities did not become faster and more accurate over time in contrast to TD children. [48]

From domain general processes to domain specific outcomes

Although recent studies have investigated how performance in WS changes over time, in order to really understand the strengths and weaknesses of the WS cognitive profile and how these develop over time one needs not only to trace these developmental trajectories back to infancy but also evaluate how domain general processes influence domain specific outcomes. [8,35]

Visual exploration is important during a number of learning processes, especially early in life as it allows infants to explore their environment before their motor abilities have developed sufficiently to explore through grasp and touch. Visual exploration can occur without moving ones' eyes or head (covert attention) but the greatest processing advantage happens by moving our eyes around (ie through saccades) and fixating on places and objects within our environment (overt attention). Saccades do not happen at random but where and when the eye will move to is influenced by properties of the stimuli (bottom-up influences) as well as by the goals and interests of the viewer (top-down effects). [51] In addition, eye movements are coupled to attention processes in that a position is fixated upon (stimulus orienting), then processed (sustained attention), and then disengaged from (attention disengagement). According to the *oculomotor readiness* hypothesis attention and eye movements are strongly related to each other as where the eyes focus is generally also where attention is shifted to and attention and eye movements are controlled by the same brain structures that are responsible for oculomotor control. [52] Thus, in order to visually explore their environment infants must learn to attend to objects and shift their attention to the appropriate objects at the appropriate time. The ability to shift attention and make prompt saccades from a fixated target to a newer target under conditions of competition (ie when both targets are present) develops from the age of 3-4 months onwards in TD infants. [53] Failing to make appropriate saccades, whether through attention or oculomotor difficulties, would result in infants not being able to scan their environments properly which impacts on the development of higher cognitive abilities. Indeed, recent studies in Autism Spectrum Disorders (ASD) have found evidence that the atypical scanning of faces and social scenes later on in life can be linked to saccadic eye movement deficits in infancy[54] and thus abnormal patterns of fixations can be used as a marker during early development for developmental disorders. [55]

Studies that have investigated eye movements in WS have shown that these are impaired from infancy onwards. Using a double-step saccade paradigm, Brown and colleagues[56] found that while toddlers with WS have sustained attention similar to chronological and mental-age matched TD controls, they had problems orienting to a target as well as making a second saccade. Also adult participants with WS demonstrated difficulties with eye movements for targets that appeared suddenly during a backwards step saccade-adaptation task. [5] In the backwards step saccade task participants were presented with a target dot on the left of the screen followed by a second dot on the right of the screen. However, during the test trials the position of the second dot was moved slightly towards the middle of the screen whilst participants were making a saccade towards it, therefore evoking a saccadic adaptation. Although 16 out of the 24 participants showed evidence of saccadic adaptation, all participants showed difficulties with moving their eyes accurately towards the second target. Karmiloff-Smith and colleagues[57,58,59] have argued that these differences in saccadic movements early on in life may affect how infants with WS learn from their environment and can be linked to cognitive outcomes later on in life. In addition, impaired abilities to plan or execute eye movements might explain the “sticky fixation”, or an inability to disengage attention from a previously fixated target to a new target, that has been observed in WS. [27,60] For example, in an eyetracking study it was found that toddlers with WS produced fewer voluntary eye-movements in an anti-saccade task, in which participants have to ignore a cue that appears on the opposite side of where the stimulus will appear, due to difficulties disengaging from the central stimulus. However, they did not show any difficulties in a Posner cueing paradigm and automatically paid attention to cued targets. In addition, they were slower to orient to invalidly cued targets. [60] This shows that, although toddlers with WS have issues with planning saccades, this is not caused by difficulties in orienting attention, but rather by an inability to disengage from a previously fixed target. The following section will discuss how the inability to plan or execute eye movements, which results in “sticky fixation”, can partially explain cognitive performance including both areas of strength and weakness in face processing, language learning, visuo-spatial abilities, and number development in WS.

People often report that individuals with WS show unusual eye contact, in that they often keep smiling and staring at people’s faces during conversations..[61] Indeed, eyetracking studies have shown that participants with WS look longer at faces in both static as well as complex dynamic social scenes in contrast to TD controls. [62,63,64,65,66,67] In addition, participants with WS often focus longer on the eye region within the face. [62, 65] This fixation on faces has been argued to lead to an expertise for faces from an early age and has been argued to be caused by hypersociability in WS. [66] However, eyetracking studies have shown that individuals with WS are not faster to detect a hidden face within unrelated landscape scenes. [65] In addition, faces distract participants with WS no greater compared to controls in a visual search task and they display a similar face bias in a probe classification task. [64] Participants with WS do however show longer fixations on the faces once they have been fixated upon compared to controls. [63,65] Furthermore, a more recent study found that the prolonged gazes to faces was only present when the social information was presented in the middle of the screen near a central fixation point but not when the stimuli were shown non-centrally. [67] These studies demonstrate that the social bias in WS is likely to be caused by a difficulty to disengage from faces, which is caused by sticky fixation, rather than by hypersociability. There are currently no studies that have investigated scan paths whilst participants with WS were administered an upright/ inversion task. Yet, a dysfunctional scanning ability whereby sticky fixation prevents backwards and forwards saccades between the different features of a face could explain the atypical local processing of features in WS. Indeed, research in TD and ASD populations have shown that eye gaze between facial features allows for a holistic processing of faces which impacts on facial recognition. [68,69]

Research in TD children has revealed that joint attention, or the ability to attend to an object or event vis-à-vis a communication partner has an important role for early language development in that it is thought to help children identify the intended referent of the parent's language and aid word-object mappings. [70] Studies in infants with WS have shown that joint attention abilities are impaired[71] in that they are less likely to initiate joint attention than mentally matched controls. [27] In addition, they were impaired in responding to joint attention, such as following where the examiner was pointing to, and this impairment predicted their language comprehension and production scores as measured by the MacArthur Communicative Development Inventories (CDI). [27] Although this study did not directly recorded eye movements of the participants, it is possible that the failure to respond to pointing gestures is caused by an inability to disengage from the experimenter's face due to sticky fixation. Eye gaze plays an important role in the ability to respond to joint attention as shifts in eye gaze trigger a shift in orientation in order to align attention between individuals. [72] There are only two studies thus far that have evaluated gaze behavior in WS but both have identified that gaze following is impaired in this population. [73,74] A study by Tsirempolou et al.[74] tested 11 participants with WS and found that adults and adolescents are impaired in following eye gaze direction and rely longer on head orientation to identify where people are looking, compared to TD children. A recent study examined eye movements while children and adults with WS aged 8 to 28 years old viewed pictures during a free-viewing condition as well as during a cued condition in which participants were asked to detect the target of an actor's gaze. [73] Participants with WS followed gaze in a similar way to controls matched for non-verbal ability when explicitly cued for, but their atypical prolonged fixation on the faces prevented them from accurately identifying the correct target. Thus, the fact that WS have difficulties in shifting their attention away from faces is likely to impair their gaze behavior which impacts joint attention abilities with further cascading effects for their word-object mapping and early vocabulary acquisition abilities.

The studies discussed thus far have shown that participants with WS show longer fixations on faces due to sticky fixation. It can be argued that the failure to disengage from faces is caused by hypersociability rather than a problem with saccade movements per se (although see discussion above). However, participants with WS have also been found to show evidence of sticky fixation on tasks that do not involve any social aspects. For example, a study investigating the scanning patterns in a few infants with WS while they were looking at large numerical displays demonstrated that they only looked at a few dots and did not scan the entire display. [58] This suggests that the inability to plan eye movements in WS causes them to only scan individual dots rather than the entire quantity and this leads to failure to discriminate between large numerosities and impacts on the development of the magnitude system and numberline, as well as the development of their precise mathematical abilities. [58,59]

As discussed above individuals with WS show difficulties in visuo-spatial production tasks such as drawing tasks and block construction tasks and this could not be attributed to sensory vision problems. [75] For example, when asked in the NAVON task to copy large letters (eg H) that are made-up of small letters (eg z), participants with WS are more likely to copy a few of the small letters that make up the large letter rather than the large itself. Earlier explanations that this impairment is caused by a local-processing bias have been refuted as no such bias has been reported in tasks where participants had to recognize rather than reproduce the stimuli. [76] An alternative explanation could be that the inability to plan eye movements impairs the number of fixations people with WS make on a target as well as the gaze-frequency (the switching between two targets) and this impairs task performance. Indeed, a recent study has illustrated that participants with WS looked less frequently at the model when copying a house compared to MA matched controls. [77] This has been argued to be caused by poor switching between the copy and the model as a result of poor eye movement planning. Looking less frequently to the model results in a higher working memory load, as one has to remember more elements when drawing which causes atypical disoriented drawings. However, this study used button presses as a proxi for fixations on the model instead of traditional eyetracking techniques. Thus, it is unclear where participants were looking during the task and whether they showed any evidence of sticky fixation. To date, only one study has investigated eye movements during a block design task using eyetracking methodology. This study also demonstrated that children with WS fixated on models as well as their partial solutions less frequently than IQ matched control children and TD adults. [78] Again, this study failed to examine the average length of fixations and cannot provide any firm support for the suggestion that the infrequent fixations towards the model are caused by sticky fixation. In addition, Hoffman and colleagues[78] argue that due to the fact that participants with WS still made errors once they had fixated the model, provides evidence that atypical looking alone cannot explain the errors made. Instead of being the cause for low accuracy, atypical looking might be the result of participants' prediction that they would fail the task anyway. As described below, task performance relies upon a number of cognitive, behavioral, and environmental factors and thus it is likely that poor eye movement planning alone cannot explain the performance on visuo-spatial block design tasks. Indeed, it cannot explain why difficulties with eye movement planning can produce difficulties in production but not perception tasks. Nevertheless, sticky fixation may also provide an explanation for the atypical neural performance observed during visual illusions. Studies in TD participants have illustrated that the N1 component is sensitive to illusory contours in ERP studies and that an increase in N1 amplitude relates to a global search relative to a local search. [79] In addition, TD participants often make a number of successive fixations at various spatial locations to enhance the visual illusion and it thus it is important to combine the information from these different saccades. [80] As mentioned before, Grice and colleagues have shown that, although participants with WS can perceive visual illusions similarly to TD controls, the neural mechanisms that support this ability are atypical. [40] Currently, no eyetracking studies have examined eye movements during illusion perception tasks in WS. However, it is possible that the fact that no differentiation was found in N1 amplitude between the different stimuli in

WS, in contrast to controls, might suggest that participant with WS fail to use a global strategy, probably caused by the fact that they only make a single fixation. [40] If this is the case, it would show that although behavioral outcomes for perceptual tasks are similar to controls, the low-level visual processes that support higher-level processing are impaired in WS.

Current limitations and future studies

Although deficient eye movement planning resulting in sticky fixation can explain a number of strengths and difficulties observed in the WS cognitive profile, research remains limited in that studies often included small sample sizes and there is a lack of longitudinal as well as developmental studies that have investigated eye movements during task performance from infancy onwards. Studies investigating eye movements from infancy onwards across development are necessary in that, even when we know that the scanning patterns in WS infants are atypical for a certain type of stimuli, different developmental outcomes are possible. For example, individuals with WS might develop compensatory strategies. Alternatively, their scanning abilities might be merely delayed or remain atypical throughout development. Thus far studies have shown that scanning paths remain atypical in WS for social stimuli[63,64,65], yet research including eyetracking with non-social stimuli is still limited. In addition, most of the existent studies have included only a small number of participants, often from a wide age range, which might explain the large variability in the data and also why some studies did not find any evidence of atypical scanning or difficulties to disengage when using social stimuli in WS. [81,82,83] Comparing eye movements on social and non-social stimuli will further our understanding of how hypersociability and attention difficulties in general contribute to atypical scanning patterns.

In addition, there are methodological issues that make comparisons between studies difficult including the different kind and method of eyetracking, as well as different analyses (see [84] for a discussion). For example, while some studies tracked participants' eyes at 250hz, others have used much lower frequencies (eg 60 or 120hz), therefore, relying on fewer samples of where the eyes were positioned within a certain time frame. Also the type of stimuli, for example whether static versus dynamic scenes were used, has been found to affect scanning paths in WS. [64]

It is also possible that abilities that seem to be unrelated in adulthood are related in infancy and can explain some aspects of the WS cognitive profile. For example, research has shown that infants with WS focus on auditory input. [34] Thus, upon hearing their mother's voice infants will turn to her upon which they will see their mother's face. It is therefore possible that the fascination with faces in WS stems from a focus on auditory stimuli combined with problems with visual disengagement and a heightened social drive. Although it is possible that such domain specific abilities explain to an extent the face and language processing abilities, there is limited evidence that hypersociablity alone can explain the atypical behavior observed on non-verbal tasks. Recent studies have shown that the atypical scanning paths for social stimuli in WS are related to their anxiety and social reciprocity. [82] Thus, future studies should not only focus on eye momevents but on a number of domain general factors as well as environmental factors. For example, numerical abilities depend on verbal abilities, visuo-spatial abilities, attention, working memory, anxiety levels and environmental influences. Therefore, any deficit in one or more of these domains from infancy onwards can affect numerical abilities later on in life.

Finally, with exception of motion perception[85,86], very few studies have investigated the oculomotor system in WS directly and it is unclear how stimulus-driven factors such as colour[87], luminance, and visual clutter influence fixation duration in WS. However, it has been shown that adults with WS have a less efficient oculomotor system that results in large saccadic variability. [5,88] Yet, saccades did improve during a saccade adaptation task, which suggests that individuals with WS would benefit from training programs aimed to improve saccadic control. Such training studies should be aimed at young participants with WS as a recent review has shown that, although there are not many training paradigms that improve attentional control with positive transfer to other cognitive abilities, training studies aimed at younger participants reported more widespread transfer of training effects. [89]

Conclusion

Individuals with WS often show an uneven cognitive profile in which language and face processing abilities are better in comparison to number and visuo-spatial abilities. However, developmental studies have shown that this uneven cognitive profile is the outcome of a number of atypical developmental processes. Specifically, atypical domain general processes, such as sticky fixation which results from problems with saccade planning, influence and interact with specific cognitive developmental processes from infancy onwards. There is probably a very complex relationship between attention and the cognitive processes described above and it is certain that other domain general factors such as executive functioning, auditory processing and other low-level visual abilities play a role in the language, face processing, number and visuo-spatial development in WS. Yet, the current overview has shown that differences in one such domain general ability, ie scanpaths in infancy, can explain a number of behavioral outcomes observed in adults with WS. This is very promising for training studies in that it was found that, although they have problems with saccade planning, participants with WS demonstrated saccadic adaptation which shows that they do have the capacity for saccadic motor learning and that their oculomotor system can be trained. [5]

Nonetheless, the number of eyetracking studies providing concrete evidence about eye movements in WS is still limited and there is a lack of developmental studies examining the role of eye movements in cognitive processes from infancy onwards. Such research is needed in order to fully appreciate the importance of saccadic movements in relation to the uneven cognitive profile in WS, especially as not all studies have found evidence for sticky fixation in WS. Therefore, large studies are required that allow the investigation of sub-types and examine the individual differences within the WS cognitive profile and how these relate to their fixation patterns.

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