Williams syndrome: Reduced attention to other's eyes in a hypersocial phenotype

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Abstract. Williams syndrome (WS) is a rare genetic disorder which leads to high social motivation as well as intellectual disability and difficulties with social interaction. Attention to others' eyes is crucial for social understanding. Individuals with WS are typically highly attentive to faces, but there is a lack of knowledge about how they attend to other's eyes, and the mechanisms underlying potential alterations in behavior. It has been suggested that physiological hypo-arousal enables individuals with WS to maintain their gaze longer at other's faces. The aim of this study was to better understand if there is atypical gaze behavior among individuals with WS which might underlie their reduced social understanding and related difficulties with social interaction.

We examined the speed and likelihood of gaze shifts to and from other's eyes in individuals with WS ($n = 37$; mean age 23 years), and controls ($n = 167$) in stratified age groups (7 months, 8-12 years, 13-17 years, adults). Peak saccadic velocity was studied as an index of arousal. Individuals with WS were less likely, and slower, to orient to the eyes compared with typically developing controls in all age groups from eight years of age but did not differ from 7-month-old infants. Peak saccadic velocity was reduced in WS, replicating previous results of hypo-arousal. The results were supported by both frequentist and Bayesian statistics. Despite the hyper-social behavioral phenotype, WS is associated with reduced attention to others' eyes. This could contribute to the difficulties with complex social interaction observed in WS.

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Williams syndrome (WS) is a rare genetic disorder occurring in around 1 in 7500 live births caused by a deletion of ~25-28 genes at chromosome 7q11.23 [1]. WS is characterized by intellectual disability, short stature, cardiovascular anomalies, distinctive facial appearance, joint laxity and other connective tissue abnormalities. The syndrome is also associated with a personality characterized as “hyper-social” [2]. For example, individuals with WS are often described as overly friendly and likely to approach strangers, showing excessive social interaction and being highly empathetic [2, 3]. Observational studies show that WS individuals preferentially direct their attention to social stimuli such as faces and voices [4–6]. Increased attention to faces is seen already in toddlerhood, and continues throughout development [2, 7, 8].

Enhanced social attention in WS comes together with relative strengths in some areas of social perception [2, 9, 10]. These strengths are particularly striking since WS is also associated with mild to moderate intellectual disability and particular challenges in areas such as visuospatial reasoning, memory and attention [11–14]. WS has been the focus of interest of researchers from many disciplines, since this uneven cognitive profile indicates a dissociation between the social brain and mechanisms involved in domain-general learning [9, 15]. Genes commonly deleted in WS have been linked to sociability in the general human population, and even in other species such as domesticated dogs [15–17].

Deletions at the WS locus lead to altered functioning of a number of neural systems important for social functioning, including the oxytocin system, the orbitofrontal cortex and the corpus callosum [15, 18, 19]. WS is also associated with both structural and functional alterations within the amygdala [20] and altered connectivity between the amygdala

and the visual and orbitofrontal cortex [19, 21]. Recently, studies of induced pluripotent stem cells (iPSCs) have shown increased apoptosis, morphologic alterations including longer total dendrites and increasing dendritic spine number and an increase in calcium transient frequency and synchronized activity likely due to increased number of dendritic spines and synapses[22].

WS has often been contrasted with autism spectrum disorder (ASD), which is typically associated with reduced social motivation, but relatively preserved visuospatial cognitive abilities [15]. However, despite their high level of sociability, individuals with WS face multiple challenges related to social interaction which sometimes overlap with those seen in ASD. For example, they often have difficulties understanding others' intentions [23] or gaze direction [24, 25]. WS is also associated with a face processing style based on individual features rather than configural properties [26–28] (but see[29]). The wide range of difficulties with face processing in WS may be surprising, given their high sociability and interest in faces. A possible explanation for this apparent contradiction is that they fail to process information within certain highly informative facial regions, such as the eyes.

The eye region is arguably the most informative part of others faces for detecting information such as emotional states and intentions. Consistent with this, humans allocate the major part of their gaze to the eye region during face viewing [30], and perceived eye contact is typically experienced as rewarding [31]. A bias to attend to eyes is observed during the earliest stages of visual attention. Eyes attract quick and automatic gaze shifts from infancy and onwards[32, 33], a process believed to be supported by a specialized brain network including the amygdala [33, 34], a brain region with altered functional and structural properties in WS [19, 20]. Altered eye contact is observed already during the earliest time stages of processing in disorders affecting social interaction such as social anxiety disorder [35] and autism [36]. To understand eye-contact processing in WS, it is therefore important to use methods with high temporal resolution, such as eye tracking.

Previous studies of eye contact in WS indicate an atypical profile, though the details of those atypicalities remain unclear. A number of studies have suggested that individuals with WS attend longer to other's eyes than their typically developing peers do, indicated by observational [2], as well as experimental studies [4, 6]. At the same time, unusual responses to eye contact have been reported for example using the Autism Diagnostic

Observation Schedule (ADOS-2; Lord et al., 2012). Klein-Tasman et al (2009) reported unusual eye contact in 50% of a group of young children (2.5-5.5 years) with WS. Unusual eye contact as operationalized in the ADOS-2 includes behaviors such as avoidant as well as overly increased eye contact or poor integration of eye contact with other communicative behaviors. It is therefore not known from previous studies whether the previously observed pattern of increased attention to faces in WS is also found for the eye region specifically.

Why would individuals with WS look at others' eyes for an extended time? At least three, not mutually exclusive, explanations are possible. First, WS may be associated with domain-general difficulties in attention disengagement [38] which could lead to prolonged gaze to eyes once the eyes are fixated [4, 6]. Secondly, individuals with WS could be quicker to detect and orient to others' eyes, although not necessarily slower in reorienting. Only one study has directly tested these first two hypotheses. In a small sample ($n = 16$), Porter et al (2010) found that, in support of the first hypothesis, individuals with WS took longer time to disengage their gaze from others' eyes once they were fixated [39]. In contrast, no evidence for quicker orienting to the eyes was found, contradicting the second hypothesis. Other studies examining attention to whole faces (but not eyes specifically) have also reported evidence for delayed disengagement rather than quicker orienting [39–41], but have not been able to distinguish between these two processes in relation to the eye region specifically. A third possible explanation is that increased gaze to eyes in WS is due to reduced physiological arousal [5, 42]. Studies in neurotypical populations have shown that direct gaze increases arousal [31], and that gaze aversion can serve as a means of arousal regulation [43]. Previous studies have hypothesized that individuals with WS may be able to hold eye contact for longer periods because lower arousal in this population reduces the need for gaze avoidance [5].

The first aim of the current study was to examine orienting to, and disengagement from, the eyes in individuals with WS. Secondly, we tested the hypothesis that increased attention to the eye region by individuals with WS is associated with hypo-arousal. Due to the well-known theoretical problems associated with selecting appropriate matched control groups in studies of participants with reduced intellectual ability, we compared WS individuals to typically developing individuals across a large age range from infancy to adulthood. This approach allowed us to map the developmental trajectories of the WS participants, as well as deviations from the neurotypical developmental trajectory. Eye

tracking was used to enable spatially and temporally precise measurements of visual attention. Sample sizes in previous eye tracking studies of WS have been small, typically including fewer than 20 participants, which limits conclusions that can be drawn. To avoid this shortcoming, we recruited a relatively large group of participants with WS ($n = 41$ tested; $n = 37$ in the final sample) in a broad age range.

Hypotheses

We hypothesized that individuals with WS would be more likely and quicker to orient to eyes than typically developing individuals (*hypothesis 1*), and that they would be less likely and slower to orient from the eyes than the typically developing groups (*hypothesis 2*). We also hypothesized that WS would be associated with hypo-arousal during social perception compared to the typically developing groups (*hypothesis 3*). We tested this hypothesis by comparing *peak saccade velocity* between WS individuals and typically developing controls. The peak of the saccadic velocity is a sensitive measure of tonic arousal, which is reduced in individuals with disorders causing low tonic arousal, as well as in healthy participants after arousal-reducing manipulations such as sleep deprivation or pharmacological manipulations targeting the arousal systems of the brain [44].

We expected all groups to show a bias to attend to eyes, manifesting as 1) shorter latencies for gaze shifts from mouth to eyes than from eyes to mouth; 2) greater likelihood of gaze shifts from mouth to eyes than from eyes to mouth. We further hypothesized that typically developing individuals would show an increased bias to attend to eyes with increasing age, but that this developmental change would not be seen in WS.

Stimulus images of actors displaying either a happy, angry, or neutral expression are included to examine whether the expected results generalize across emotional expressions.

Pre-registration

The hypotheses and analysis plan were pre-registered prior to data analysis (link: <https://osf.io/ybt65/>).

Methods

Participants

Individuals with WS (final $n = 37$; mean age = 23, SD = 12) were recruited through the Center for Rare Diseases at Karolinska University hospital, Ågrenska – a national centre of competence for rare diseases in Sweden and through contact with patient organizations. All participants had been diagnosed with Williams syndrome in specialized health care. Since many individuals were diagnosed early by *Fluorescent in situ hybridization* (FISH) there was no information about the size of the deletion available in most adults. The individuals included in this study are all part of a larger ongoing study about WS. To date, 24/41 included individuals included in our study have been extensively investigated. Venous blood and urine sampling have been conducted to determine standard routine blood parameters and to detect endocrine abnormalities, hypercalcemia, and impaired glucose tolerance and fibroblasts (12 individuals) have been taken for DNA analyses, RNA-based studies and for the establishment of an iPSC-NE model for WS (4 individuals) to reveal mechanisms behind neural dysfunction. The 24 individuals with WS also completed an extensive clinical investigation, a cognitive assessment and a diagnostic interview for anxiety disorders with a clinical psychologist. IQ was assessed using the Wechsler Adult Intelligence Scale, 4th Ed. (WAIS-IV[45]) or the Wechsler Intelligence Scale for Children (WISC-V[46]), depending on the participant's age. The remaining individuals ($n = 18$) were tested in a temporary lab facility but did due to Covid-19 not yet complete additional assessments. In addition, 5/41 individuals were excluded because of a lack of valid data (see *Data Processing*).

Infants (final $n = 37$; mean age 7 months, SD = 0.20 months) were recruited from a database of families expressing interest in developmental research. Exclusion criteria were known or suspected medical or developmental concern, premature birth, or a family history of genetic syndromes or neurodevelopmental disorders up to second degree relatives. Two additional infants were excluded because of a lack of valid data (see *Data Processing*).

Typically developing children and adolescents (final $n = 80$, age 10-17 years) completed the task as part of control groups for two other studies. The first group ($n = 39$, mean age 12 years, SD = 2.64) was initially recruited from a database of families expressing interest in participating in developmental research and included as a control group in studies of ADHD. Details about the sample are reported in previous publications [47, 48]. The second group ($n = 41$; mean age 14.28, SD = 2.43) were recruited from the Swedish tax registry (for details about the sample, see [35]) and initially included as a control group in a study on

social anxiety disorder. Participants had no medical or psychiatric diagnoses according to parental report. In the second group, this was confirmed through a diagnostic interview with a clinical psychologist using the MINI-KID [49]. For analytic purposes, the child sample was split into two age groups (8 – 12 years old and 13 -17 years, henceforth child and adolescent groups respectively).

Typically developed adults ($n = 50$; mean age 34; $SD = 11$) were recruited through a database of individuals who had expressed interest in participating in research experiments. The typically developed adults had no current medical diagnoses and were not taking any psychotropic medication. A semi-structured psychiatric interview was conducted with a clinical psychologist using the Mini International Neuropsychiatric Interview (MINI [50]).

Age, gender, and average number of valid trials per group are shown in *Table 1*. The WS and infant groups completed a smaller number of valid trials than adults and adolescents in the eyes primed condition ($p < .01$), and a smaller number of trials than children, adolescents, and adults in the mouth primed condition ($p < .01$). As can be seen in *Table 1*, the gender proportion was uneven in the child and adolescent control groups reflecting recruitment choices made in the original studies where these individuals were included. Preliminary analyses showed no effect of gender on any of the dependent variables (all $p > .25$), and we therefore chose to include all participants in these groups instead of making a stratified selection based on gender.

Ethical Approval

The study was approved by the Regional Ethics Committee of Stockholm, Sweden (dnr 2018/1218-31, amendment 2019-08-06). The recruitment of the child and adolescent groups was conducted in accordance with ethical approvals by the Regional Ethics Committees of Stockholm and Uppsala.

Table 1. Age, gender, and number of valid trials

	WS	Adults	Adolescents	Children	Infants
N	37	50	36	44	37
% Female	46%	48%	21%	71%	43%

Age in years: M, (SD), [min- max]	23.43 (12.24) [9.00-53.00]	34.17 (11.41) [18.65-62.79]	15.54 (1.25) [13.10-17.30]	10.67 (1.27) [8.25-12.80]	0.58 (0.02) [0.55-0.62]
Valid trials: M, (SD), [min- max]					
Eyes cued	18.99 (7.71) [6 - 30]	29.28 (1.26) [25 -30]	28.72 (2.22) [22 -30]	25.04 (6.42) [7 -30]	15.59 (7.13) [5 – 28]
Mouth cued	19.92 (8.24) [6 - 30]	27.72 (2.56) [20 - 30]	25.61 (5.43) [8 – 30]	22.76 (6.45) [5 – 30]	18.64 (6.67) [5 – 30]

Power Analysis

A power analysis was conducted using the package *simr* [51] in R[52]. This analysis indicated that the study had above 80% power to detect small-to medium effect sizes (marginal $f^2 = 0.15$).

Data Recording

Data were recorded using Tobii corneal reflection eye trackers (Tobii inc, Danderyd, Sweden) at a sample rate of 120 HZ in the WS, healthy adult, adolescent, and infant groups. Data from children were recorded at a sample rate of 60 HZ ($n = 39$), or 120 HZ ($n = 41$).

Data Processing

Fixations and saccades were identified using an I-VT filter implemented in MATLAB with velocity threshold criterion set to 30 degrees per second. To measure peak saccade velocity, data were first up-sampled to 1200 HZ using a simple spline function, following previous publications [53]. Saccadic velocity profiles are distorted if recorded at sample rates below 200 HZ. However, it has been shown that peak velocities can be estimated with adequate precision in data recorded at 120 HZ or above after up-sampling [53]. Data sampled at 60HZ were not included in the peak velocity analyses. Individuals contributing less than five valid trials to a condition were excluded from further analyses of that condition.

Experimental task

Stimuli were images of human faces from the Karolinska Directed Emotional Faces dataset [54], cropped to include only the inner region of the face (see Figure 1). The depicted actors (5 male, 5 female) displayed an angry, happy, or neutral facial expression. Each actor appeared an equal number of times displaying each emotion. The experimental

paradigm included 60 trials, equally distributed between two conditions. Trials began with a fixation cross presented on a uniform gray background for 1 second before the stimulus image appeared. In 50% of the trials, stimulus images were subsequently presented so that participants' initial point of gaze was within the eye region (henceforth: the *eyes cued condition*). In the other 50% of the trials, stimuli were instead presented so that participants' point of gaze was within the mouth (henceforth: the *mouth cued condition*). Stimulus images remained on screen for 1.5 seconds. Participants were asked to attend to the screen but were not given any further instructions and therefore this was a free viewing task.

Figure 1. Overview of the experiment. In 50% of trials (A), a fixation cross presented for 1 second was followed by an image of a face with the mouth aligned to the fixation cross (the *mouth cued condition*) presented for 1.5 seconds. On 50% of the trials (B), the face was instead presented with the eyes in the position of the fixation cross (the *eyes cued condition*). The position of the fixation cross is shown overlaid on the face stimuli for illustrative purposes.

Dependent variables

The dependent variables were 1) the proportion of mouth-cued trials with a gaze shift towards the eyes; 2) the proportion of eyes-cued trials with a gaze shift away from the eyes; 3) the latency to orient to the eyes in the mouth-cued condition, and 4) the latency to

orient away from the eyes in the eyes-cued condition; and 5) peak saccade velocity divided by saccadic amplitude to account for the fact that the distance and velocity of a saccade are typically closely correlated. All saccades with an amplitude exceeding 4 degrees detected during a trial were included in this metric, regardless of their direction. Preliminary analyses showed that the latency to orient to the non-cued facial region was highly correlated with the latency to orient from the cued region to any location ($r = .86$, $p < .0001$), indicating that first saccades landing outside the eye or mouth area were very rare. In line with previous studies (e.g. [35, 55]), saccades landing outside any of the cued areas were therefore not included in the analyses.

Statistical Analyses

Data were analyzed using linear mixed-effects models with random intercept for participant (i.e. treating observations from the same individual as repeated measures). Statistical analyses were conducted in MATLAB using the functions *fitlme* and *compare*. Data were analyzed using both conventional frequentist (i.e. null hypothesis testing) and Bayesian statistics. Statistical significance was tested by comparing a model including the effect of interest (i.e. *group*) to the next most complex model (the null model) without this effect [56]. A Bayes factor (BF) was calculated from the Bayesian Information Criteria (BIC) values of the two models following Wagenmakers (2007) using the formula:

$$BF_{10} = \exp^{(BIC_{H0} - BIC_{H1})/2}$$

The BF quantifies the relative probability of the hypothesis (the model including the effect of interest) and the null (the same model without this effect). By convention, a $BF > 3$ indicates positive evidence for the hypothesis, a $BF > 20$ indicates strong support, and a $BF > 150$ very strong support [57]. By reversing the terms, a BF_{01} can be calculated, where larger numbers indicate higher probability of the null. The main strengths of Bayesian as compared to frequentist statistics is that it is less vulnerable to type I errors, and that it allows researchers to conclude that the null hypothesis fits the data best [57]. Effect sizes of the fixed effects are reported as unstandardized b coefficients and standardized marginal f^2 [58], which reflect the proportional increase in explained variance that the fixed effect of interest contributes relative to the null model. The alpha level was set to .05. All significant results survived correction for multiple comparisons with the Benjamini-Hochberg procedure with a false discovery rate of .05. Uncorrected p-values are reported.

Results

Proportion of first gaze shifts. An initial omnibus model including data from both WS and TD individuals showed a significant effect of cued region, reflecting that the proportion of gaze shifts was higher to, than from the eyes ($\chi^2 = 27.55$, $p < .001$, $b = 0.16$, $SE = 0.03$, $BF_{10} > 500$, $f^2 = 0.09$). There was a main effect of group ($\chi^2 = 17.11$, $p = .002$, $BF_{10} = 397$, $f^2 = 0.04$), and an interaction effect between group and cued region ($\chi^2 = 44.13$, $p < .001$, $BF_{10} > 500$, $f^2 = 0.27$). Follow-up tests showed that groups differed in the proportion of gaze shifts to the eyes ($\chi^2 = 71.23$, $p < .001$, $BF_{10} > 500$, $f^2 = 0.43$; see Figure 2). In contrast, no significant effect of group was found on the proportion of gaze shifts away from the eyes ($\chi^2 = 9.12$, $p = .058$, $f^2 = 0.05$), and the Bayesian analysis strongly supported the null hypothesis ($BF_{10} = 401.17$). Significant main- and interaction effects were followed up to address the specific hypotheses as described below.

Is there a preference for eyes in typical development? Gaze shifts towards the eyes were more likely than gaze shifts away from the eyes in the adult, adolescent, and child groups (all $p < .001$, all $BF > 500$). In contrast, infants showed the opposite pattern - i.e. a preference for orienting away from, rather than to the eyes ($\chi^2 = 4.18$, $p = .041$, $b = 0.13$, $SE = 0.06$, $BF_{10} = 1.53$, $f^2 = .09$).

Does orienting to eyes change during typical development? As can be seen in Table 2 and Figure 2, the probability of orienting towards the eyes increased in typically developing individuals from infancy to childhood, and from childhood to adolescence, but remained stable between adolescence and adulthood. The proportion of gaze shifts to the eyes was not related to age in the WS group ($\chi^2 = 0.03$, $p = .865$, $BF_{10} = 0.17$, $BF_{10} = 5.83$, $f^2 < 0.01$).

Is there an altered preference for eyes in WS? No significant difference in the proportion of gaze shifts to and from the eyes was found in the WS group ($\chi^2 = 0.01$, $p = .953$, $f^2 < .01$), and the Bayesian analysis supported the null hypothesis ($BF_{10} = 0.16$, $BF_{01} = 6.23$).

As can be seen in Table 3 and Figure 2, individuals with WS were less likely to orient to the eye region than typically developing children ($\chi^2 = 7.36$, $p = .007$, $BF_{10} = 4.25$), adolescents ($\chi^2 = 13.06$, $p < .001$, $BF_{10} = 85.15$), and adults ($\chi^2 = 27.08$, $p < .001$, $BF_{10} > 500$).

Individuals with WS were marginally more likely to orient to the eyes than infants ($\chi^2 = 4.23$, $p = .040$, $BF_{10} = 0.97$), but the difference was not statistically significant after correction for multiple comparisons, and the Bayes factor was inconclusive.

The proportion of gaze shifts to the eyes was not related to age in the WS group ($\chi^2 = 0.07$, $p > .50$, $BF_{10} = 0.17$, $f^2 < 0.01$).

Does emotional expression affect the probability to orient to eyes? Individuals with WS were less likely than typically developed adults and adolescents to orient to the eyes of faces with each of the included emotional expressions (all $p < .01$, all $BF_{10} > 15$). Differences between the WS group and children were significant for happy and neutral, but not angry faces. No group differences were found between individuals with WS and infants (see *Supplementary materials*).

Figure 2. Probability of gaze shifts to the eyes (left) and from the eyes (right) by group. WS = Williams syndrome; *** $p < .001$. Asterisks show significant difference between WS and other groups. Error bars show 95% confidence intervals.

Group Comparison	Model comparison χ^2	p	b	SE	BF ₁₀	BF ₀₁	f ²
WS vs. Infant	4.23	.040†	-0.14	0.07	0.97	1.03	0.06
WS vs. Child	7.36	.007**	0.13	0.05	4.25	0.24	0.09
WS vs. Adolescent	13.06	<.001***	0.20	0.05	85.15	0.01	0.22
WS vs. Adult	27.08	<.001***	0.22	0.04	>500	<0.01	0.37
Infant vs Child.	23.09	<.001***	0.27	0.05	>500	<.01	0.31
Child vs. Adolescent	3.78	.052	0.07	0.04	0.75	1.33	0.05
Adolescent vs. Adult	0.64	.425	0.02	0.03	0.16	6.43	0.01

Table 2. Pairwise group comparisons of the probability of gaze shifts to the eyes. *** $p < .001$; ** $p < .01$; † Non-significant after correction for multiple comparisons; WS = Williams syndrome; BF₁₀ = Bayes factor favoring the hypothesis; BF₀₁ = Bayes factor favoring the null

Latency to first gaze shifts. Results from the analyses of saccadic latencies mirrored the findings from the analyses of proportion of first gaze shifts. An initial omnibus model including data from both WS and TD individuals showed a significant effect of cued region, reflecting quicker gaze shifts towards the eyes than away from the eyes ($\chi^2 = 46.99$, $p < .001$, $b = 199$, $SE = 27$, $BF_{10} > 500$, $f^2 = .07$). There was also a main effect of group ($\chi^2 = 90.90$, $p < .001$, $BF_{10} > 500$, $f^2 = .08$), and an interaction effect between group and cued region ($\chi^2 = 27.86$, $p < .001$, $BF_{10} = 28.03$, $f^2 = .04$).

Follow-up tests showed that gaze shifts were quicker to the eyes than away from the eyes in typically developing adults ($\chi^2 = 32.27$, $p < .001$, $BF_{10} > 500$, $b = 349$, $SE = 52$, $f^2 = .027$), adolescents ($\chi^2 = 21.88$, $p < .001$, $BF_{10} > 500$, $b = 314$, $SE = 56$, $f^2 = .035$) and children ($\chi^2 = 22.93$, $p < .001$, $BF_{10} > 500$, $b = 233$, $SE = 43$, $f^2 = .012$).

In contrast, no consistent preference was found in WS ($\chi^2 = 0.23$, $p > .50$, $BF_{10} = 0.19$, $b = 37$, $SE = 76$, $f^2 < 0.01$) or infants ($\chi^2 = 0.19$, $p > .50$, $b = 23$, $SE = 54$, $BF_{10} = 0.19$, $f^2 < 0.01$). In typically-developing individuals, the latency of first gaze shifts towards the eyes

decreased from infancy to childhood, and again from childhood to adolescence, but remained stable between adolescence and adulthood.

Individuals with WS were slower to orient to the eye region than children, adolescents, and adults. They were marginally faster than infants, but the p-value did not survive correction for multiple comparisons, and the Bayes factor was inconclusive (see *Table 3 and Figure 3*). The latency to orient to the eyes was not linked to age in the WS group ($\chi^2 < 0.01$, $p = 0.969$, $b = 0.14$, $SE = 3.55$, $BF_{10} = 0.18$, $BF_{01} = 5.65$). Additional analyses showed that the WS group oriented slower than typically developing adults, adolescents, and children to the eyes of faces with each of the included emotional expressions (all $p < .001$, all $BF_{10} > 500$, see *Supplementary materials*).

To sum up, contrary hypothesis one, individuals with WS were both *less likely* and *slower* to orient to eyes than typically developing controls, and contrary to hypothesis two, did not differ from controls in the probability or latency to orient from the eyes. Whereas the expected preference to attend to eyes rather than the mouths was found in typically developing individuals above infancy, this bias was absent in individuals with WS.

Figure 3. Latencies to orient to eyes (left) and from eyes (right) by group. Error bars show 95% confidence intervals. WS = Williams syndrome; *** $p < .001$. Violins show probability density functions. Asterisks show significant difference between WS and other groups. Error bars show 95% confidence intervals of the mean.

Group Comparison	χ^2	P	b	SE	BF ₁₀	BF ₀₁	f ²
WS vs. Infant	4.12	.042†	-132.35	63.85	1.01	0.99	0.03
WS vs. Child	25.35	<.001***	236.28	43.71	>500	>01	0.12
WS vs. Adolescent	31.63	<.001***	318.93	49.69	>500	>01	0.28
WS vs. Adult	29.17	<.001***	269.93	45.92	>500	>01	0.18
Infant vs Child.	47.94	<.001***	366.88	45.26	>500	>01	0.23
Child vs. Adolescent	5.87	.015*	79.38	32.14	2.17	0.46	0.02
Adolescent vs. Adult	1.80	.180	49.34	36.60	0.28	3.59	<0.01

Table 3. Pairwise group comparisons of the latency to first gaze shift to the eyes. *** $p < .001$; * $p < .05$; † Non-significant after correction for multiple comparisons; WS = Williams syndrome; BF₁₀ = Bayes factor favoring the hypothesis; BF₀₁ = Bayes factor favoring the null

Is arousal reduced in WS during social perception?

Peak saccadic velocity differed between groups (main effect of group, $\chi^2 = 84.82$, $p < .001$, $BF_{10} > 500$, $f^2 = 0.28$). There was also a main effect of condition, reflecting higher peak saccadic velocity when the eyes were primed ($\chi^2 = 11.13$, $p = .001$, $BF_{10} = 18.29$, $f^2 = 0.01$). No interaction effect between group and condition was found ($\chi^2 = 5.95$, $p = 0.203$, $BF_{10} < 0.01$, $BF_{01} > 500$, $f^2 < 0.01$). As can be seen in *Table 4*, the WS group had reduced peak saccadic velocity, indicating reduced arousal, compared to typically developing individuals in all age ranges. In the WS group, no relations were found between peak saccadic velocity and the latency to orient from the eyes, ($\chi^2 = .08$, $p > .50$, $BF_{10} = 0.17$, $BF_{01} = 5.76$, $f^2 = 0.01$), or the proportion of gaze shifts from the eyes ($\chi^2 = 0.66$, $p = .418$, $BF_{10} = 0.23$, $BF_{01} = 4.38$, $f^2 = 0.01$), with Bayes factors favoring the null.

Group Comparison	χ^2	P	b	SE	BF_{10}	BF_{01}	f^2
WS vs. Infant	8.28	.004**	3.24	1.09	7.30	0.14	0.05
WS vs. Child	34.10	<.001***	7.65	1.09	>500	<.01	0.49
WS vs. Adolescent	42.84	<.001***	6.97	0.89	>500	<.01	0.37
WS vs. Adult	79.29	<.001***	7.31	0.64	>500	<.01	0.49
Infant vs Child.	7.58	.006**	4.44	1.55	4.69	0.21	0.12
Child vs. Adolescent	0.48	.487	-0.70	1.01	0.14	7.03	<0.01
Adolescent vs. Adult	0.30	.584	0.35	0.63	0.13	7.60	<0.01

*Table 4. Pairwise group comparisons of peak saccadic velocity (divided by saccadic amplitude). *** $p < .001$; ** $p < .01$; WS = Williams syndrome; BF_{10} = Bayes factor favoring the hypothesis; BF_{01} = Bayes factor favoring the null*

Discussion

In line with the hyper-social behavioral phenotype of WS, we hypothesized that individuals with the condition would show increased attention to others' eyes, manifesting as 1) an increased tendency to orient to the eye region of others, and 2) prolonged attention to

the eyes of others once they were fixated. These hypotheses were not supported. Instead, *reduced* attention to other's eyes was found in individuals with WS, as they were slower and less likely to orient to the eye region than typically developing individuals across a wide age range. Furthermore, whereas typically developing individuals from eight years old to adulthood showed the expected bias to orient to eyes rather than to the mouth, this bias was absent in WS across all ages. Notably, reduced orienting to eyes was found for all emotional expressions. Finally, we hypothesized that individuals with WS would show reduced arousal during social perception. This hypothesis was supported in that individuals with WS showed reduced peak saccadic velocity compared to all typically developing age groups from infancy to adulthood. To the best of our knowledge, this is the largest eye tracking study of WS to date ($n = 39$). The conclusions were supported by both Bayesian and frequentist statistics, with medium to strong effect sizes. The results are discussed below.

A largely subcortical brain network including the amygdala supports detection of eye contact and orienting towards others' eyes [33]. Our results suggest that this network is atypical in WS. At the behavioral level, our results suggest that, at the earliest time stages, WS is associated with reduced, rather than enhanced attention to eyes, which are arguably one of the most salient social stimuli for humans. This is a striking difference to observational studies which reported increased attention to eyes in WS [8], but is more consistent with a previous report of atypical eye contact in young children with WS [59]. It is also seemingly in contrast to studies reporting enhanced attention to faces (although not eyes per se) in WS [4, 5, 7, 8, 40]. It should be noted that these studies have examined social attention in situations where social stimuli compete for attention with various non-social distractors. Previous studies have also not cued participant's gaze to specific areas within the face or have not included spatially precise measures of gaze allocation such as eye tracking. Our results point to the importance of measuring social attention using high spatial and temporal resolution to improve our understanding of neurodevelopmental conditions.

The eye region conveys crucial information about other's mental states and their intentions regarding the environment. However, decoding this information requires the ability to flexibly shift one's attention between others' eyes and the surroundings [24, 60]. Disruptions to these processes could contribute to the difficulties that individuals with WS face within areas such as mental state understanding and gaze following.

Importantly, reduced orienting to the eyes could not be explained by a general slowing of attention, since no group differences were found in the latency or probability of orienting towards the mouth (and away from the eyes). Since typically developing and WS participants were highly similar in probability and latency to look away from the eyes, our results contradict the theory that altered eye contact in WS would result from domain-general impairments in attention shifting. This contrasts with a number of previous studies which suggested that enhanced attention to faces in WS stems from a reduced ability to disengage attention [5, 39, 40]. It should be noted that this null result was found despite adequate statistical power, and that the Bayesian analysis strongly favored the null.

Previous studies have suggested that tonic hypo-arousal is a factor contributing to enhanced social attention in WS. Consistent with previous studies, we found that individuals with WS executed saccades with reduced peak amplitude (indicating reduced arousal) compared to all the TD groups, including seven-month old infants. [5, 42, 61]. However, the hypothesized link between hypo-arousal and *enhanced* eye contact was not supported, as the WS group did not attend longer to the eye region before reorienting, and individuals with relatively lower peak saccadic velocity within the WS group did not take longer to reorient from eyes. Instead, hypo-arousal could be an underlying cause of reduced orienting to eyes. It is known from previous studies that hypo-arousal can impair detection and orienting of attention to salient and motivationally important stimuli [47, 62]. We suggest that hypo-arousal may have different effects of social attention depending on the stage of visual attention. Hypo-arousal may facilitate prolonged social attention once it is established [5], but also reduce the likelihood that it is established.

Our results point to a potential overlap between WS and autism spectrum disorder, which is associated with reduced orienting to social stimuli such as faces and eyes [63][64]. This similarity is interesting, given the fact that WS is also associated with increased social motivation and interest in faces, traits that are typically not seen in ASD[15]. Previous studies comparing visual attention in WS and ASD have also suggested that individuals with WS attend longer to whole faces than those with ASD, although not examining eyes specifically [4, 40]. Our results suggest that social interaction challenges in both conditions may be associated with a reduced ability to process eye gaze.

Altered visual attention to eyes in WS was not modulated by the emotional expression of the face. In fact, WS individuals showed a highly typical pattern of increased attention to the eyes of angry faces and the mouth of happy faces. This contrasts with previous studies which reported atypical attention to (whole) faces signaling positive emotional states or trustworthiness in WS [39, 65].

The inclusion of multiple control groups across a wide range enabled us to examine how individuals with WS deviate from the typical developmental trajectory in considerable detail. However, a limitation is that the WS group did not include individuals in infancy and toddlerhood, which reduces our ability to detect developmental trajectories in this population. Future studies would also benefit from comparisons between WS individuals and groups with other genetic syndromes affecting attention, cognition, and social behavior. To sum up, this study suggests that despite the highly social behavioral phenotype, WS is associated with reduced attention to other's eyes at the earliest time stages of attention. Hypo-arousal during social perception may contribute to this pattern of atypical attention. Disrupted orienting to other's eyes is likely to affect social understanding and interaction. These findings add to our understanding of the pathways from genetic deletions to altered social phenotype in Williams syndrome.

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Supplementary Materials

Group Comparison	Model comparison χ^2	P	b	SE	BF ₁₀	BF ₀₁	f ²
ANGRY							
WS vs. Adult	19.00	<.001***	0.21	0.05	>500	0.00	0.24
WS vs. Adolescent	8.51	.0035**	0.19	0.06	8.76	0.11	0.14
WS vs. Child	2.99	.0837	0.10	0.06	0.48	2.09	0.04
WS vs. Infant	2.41	.1207	-0.11	0.07	0.39	2.56	0.03
Infant vs. Child	11.88	.0006**	0.21	0.06	41.07	0.02	0.15
Child vs. Adolescent	3.29	.0698	0.09	0.05	0.59	1.71	0.04
Adolescent vs. Adult	0.42	.5146	0.02	0.03	0.14	7.14	<0.01
HAPPY							
WS vs. Adult	22.23	<.001***	0.26	0.05	>500	0.00	0.29
WS vs. Adolescent	11.71	.0006**	0.24	0.07	43.20	0.02	0.20
WS vs. Child	7.29	.0069**	0.16	0.06	4.10	0.24	0.09
WS vs. Infant	3.20	.0738	-0.14	0.08	0.58	1.73	0.05
Infant vs. Child	23.13	<.001***	0.30	0.06	>500	<.01	0.31
Child vs. Adolescent	3.89	.0485	0.08	0.04	0.79	1.26	0.05
Adolescent vs. Adult	0.32	.5689	0.02	0.03	0.13	7.51	<0.01
NEUTRAL							
WS vs. Adult	20.94	<.001***	0.21	0.04	>500	<.01	0.28
WS vs. Adolescent	9.64	.0019**	0.18	0.06	15.53	0.06	0.16
WS vs. Child	8.29	.0040**	0.15	0.05	6.82	0.15	0.10
WS vs. Infant	4.25	.0392	-0.16	0.07	0.99	1.01	0.06
Infant vs. Child	23.18	<.001***	0.30	0.06	>500	<.01	0.31
Child vs. Adolescent	0.88	.3492	0.04	0.04	0.18	5.70	0.01
Adolescent vs. Adult	0.81	.3696	0.02	0.03	0.17	5.90	0.01

*Table S1. Pairwise group comparisons of the probability of gaze shifts to the eyes for specific emotions. *** $p < .001$; * $p < .01$; * $p < .05$; WS = Williams syndrome; BF₁₀ = Bayes factor favoring the hypothesis; BF₀₁ = Bayes factor favoring the null*

Group Comparison	Model comparison χ^2	P	b	SE	BF ₁₀	BF ₀₁	f ²
ANGRY							
WS vs. Adult	18.27	<.001***	-214.52	47.92	>500	<.01	0.13
WS vs. Adolescent	20.71	<.001***	-262.78	53.20	>500	<.01	0.23
WS vs. Child	14.81	<.001***	-187.57	46.79	175.42	0.01	0.10
WS vs. Infant	2.08	.1489	100.47	68.69	0.33	2.99	0.02
HAPPY							
WS vs. Adult	26.60	<.001***	-252.16	45.28	>500	0.00	0.21
WS vs. Adolescent	19.70	<.001***	-264.24	54.81	>500	0.00	0.22
WS vs. Child	9.44	.002**	-159.57	50.57	12.03	0.08	0.06
WS vs. Infant	2.20	.138	94.78	62.72	0.36	2.80	0.02
NEUTRAL							
WS vs. Adult	33.81	<.001***	-271.53	42.55	>500	<.01	0.24
WS vs. Adolescent	29.42	<.001***	-323.10	52.85	>500	<.01	0.35
WS vs. Child	22.43	<.001***	-239.08	47.50	>500	<.01	0.15
WS vs. Infant	1.24	.2657	79.85	71.29	0.22	4.53	<0.01

Table S2. Pairwise group comparisons of the latency to first gaze shifts to the eyes for each emotional expression. *** $p < .001$; * $p < .05$; WS = Williams syndrome; BF₁₀ = Bayes factor favoring the hypothesis; BF₀₁ = Bayes factor favoring the null