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Accepted Version

McGrath, L. M., Oates, J. M., Dai, Y. G., Dodd, H. F., Waxler, J., Clements, C. C., Weill, S., Hoffnagle, A., Anderson, E., MacRae, R., Mullett, J., McDougle, C. J., Pober, B. R. and Smoller, J. W. (2016) Attention bias to emotional faces varies by IQ and anxiety in Williams syndrome. *Journal of Autism and Developmental Disorders*, 46 (6). pp. 2174-2185. ISSN 1573-3432 doi: <https://doi.org/10.1007/s10803-016-2748-y> Available at <https://centaur.reading.ac.uk/60212/>

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Published version at: <http://link.springer.com/article/10.1007/s10803-016-2748-y>

To link to this article DOI: <http://dx.doi.org/10.1007/s10803-016-2748-y>

Publisher: Springer

Publisher statement: This is the author's version of the manuscript. The final, published version is available at: <http://link.springer.com/article/10.1007/s10803-016-2748-y>

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Title: Attention bias to emotional faces varies by IQ and anxiety in Williams syndrome

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Acknowledgments: We would like to thank the participants who volunteered their time at the biennial Williams Syndrome Association conference and the Williams Syndrome Association for facilitating research opportunities at the conference. We also extend our thanks to the other research groups at the conference for working collaboratively to advance our collective research goals. *Funding:* This work was supported by an American University Faculty Research Support Grant (L.M.M.), NIH grant T32-MH16259 (L.M.M.), NIH grant K24-MH094614 (J.W.S), the Tepper Family MGH Scholars award (J.W.S), and the Nancy Lurie Marks Family Foundation (C.J.M).

Conflict of interest: The authors declare that they have no conflicts of interest.

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Abstract

Individuals with Williams syndrome (WS) often experience significant anxiety. A promising approach to anxiety intervention has emerged from cognitive studies of attention bias to threat. To investigate the utility of this intervention in WS, this study examined attention bias to happy and angry faces in individuals with WS ($N=46$). Results showed a significant difference in attention bias patterns as a function of IQ and anxiety. Individuals with higher IQ or higher anxiety showed a significant bias toward angry, but not happy faces, whereas individuals with lower IQ or lower anxiety showed the opposite pattern. These results suggest that attention bias interventions to modify a threat bias may be most effectively targeted to anxious individuals with WS with relatively high IQ.

Keywords: Williams syndrome, anxiety, attention bias, social dot-probe, emotional faces

Attention bias to emotional faces varies by IQ and anxiety in Williams syndrome

Williams syndrome (WS) is a neurodevelopmental disorder caused by a 1.5-1.8 megabase microdeletion on chromosome 7q11.23 (Pober, 2010). WS is characterized by distinctive social and cognitive features, including a hypersocial personality, mild to moderate intellectual disability, and relative strengths in verbal compared to nonverbal abilities (Mervis & John, 2010; Riby & Porter, 2010). In addition to these hallmark characteristics, studies consistently report higher levels of anxiety in WS compared to typically-developing individuals and to individuals with other neurodevelopmental disorders (Blomberg, Rosander, & Andersson, 2006; Cherniske et al., 2004; Dimitropoulos, Ho, Klaiman, Koenig, & Schultz, 2009; Dodd & Porter, 2009; Dykens, 2003; Einfeld, Tonge, & Florio, 1997; Einfeld, Tonge, & Rees, 2001; Kennedy, Kaye, & Sadler, 2006; Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, & Mervis, 2006; Leyfer, Woodruff-Borden, & Mervis, 2009; Rodgers, Riby, Janes, Connolly, & McConachie, 2012; Stinton, Elison, & Howlin, 2010; Stinton, Tomlinson, & Estes, 2012; Woodruff-Borden, Kistler, Henderson, Crawford, & Mervis, 2010). Prevalence estimates indicate that 50% or more of individuals with WS may meet diagnostic criteria for an anxiety disorder with generalized anxiety disorder and specific phobia being the most common (Dykens, 2003; Kennedy et al., 2006; Leyfer et al., 2006, 2009; Woodruff-Borden et al., 2010). From clinical reports, it is clear that anxiety symptoms can exert a major impact on quality of life for individuals with WS and are chronic in their course (Woodruff-Borden et al., 2010). Unfortunately, treatment approaches for anxiety in WS are under-developed. Cognitive-behavioral treatments for anxiety have shown some promise with adaptation for developmental

level, but the evidence is mainly limited to case studies (Klein-Tasman & Albano, 2007; Phillips & Klein-Tasman, 2009). Similarly, the efficacy of anxiolytic pharmacological agents is understudied in this population, with the evidence primarily limited to case reports or parental surveys (Martens et al., 2012; Urgeles, Alonso, & Ramos-Moreno, 2013).

A new therapeutic approach for anxiety disorders in typically-developing populations has emerged from cognitive studies of attention bias to threat that may be applicable to the WS population. In typically-developing populations, previous studies have shown that children and adults with various anxiety disorders display a differential bias toward threat stimuli compared to non-anxious controls (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & Van IJzendoorn, 2007). Computer training protocols that attempt to modify this bias have been developed as a treatment for anxiety. The theoretical rationale for these treatment protocols is grounded in the hypothesis that modification of early attentional mechanisms will prevent the cascading negative effects of hypervigilance to threat (L. K. White, Suway, Pine, Bar-Haim, & Fox, 2011).

Attention bias modification trials in children (for reviews see Lau, 2013; Lowther & Newman, 2014) and adults (for meta-analyses see Beard, Sawyer, & Hofmann, 2012; Cristea, Kok, & Cuijpers, 2015; Hakamata et al., 2010; Hallion & Ruscio, 2011; Mogoşe, David, & Koster, 2014) have showed promise (Bar-Haim, 2010; Clarke, Notebaert, & MacLeod, 2014), although there is ongoing debate about clinical efficacy (i.e., Cristea, Kok, et al., 2015; Cristea, Mogoşe, David, & Cuijpers, 2015; Emmelkamp, 2012; Mogoşe et al., 2014). Most relevant to the current study, there is some evidence for success of these training protocols for individuals with generalized anxiety disorder (Amir, Beard, Burns, & Bomyea, 2009; Mogoşe et al., 2014), one of the most common anxiety diagnoses in WS.

As a precondition to considering attention bias modification for individuals with WS and high anxiety levels, it is necessary to carefully document attention bias patterns in this population. Two previous studies have examined attention bias to threatening scenes and emotional faces in WS using the dot-probe paradigm (Dodd & Porter, 2010, 2011). Results showed attention bias to threatening scenes and happy faces, but not angry faces. The null findings for angry faces would suggest that attention bias modification based on emotional faces may not be successful for individuals with WS. However, these null findings were obtained in a small sample ($N=16$) which may have been under-powered to detect an effect.

The current study was designed to further examine attention bias to emotional faces in a larger, independent sample of individuals with WS using the dot-probe paradigm. We chose to focus on emotional faces for two reasons: (1) the majority of picture-based attention bias modification paradigms have used emotional faces as stimuli, so there is a precedent for developing training procedures with these stimuli and (2) individuals with WS are highly interested in faces, so an attention bias modification protocol with faces may be more motivating as a treatment approach compared to threatening scenes. We had two primary hypotheses. First, we hypothesized that individuals with WS would display an attention bias to happy faces (compared to neutral faces), consistent with previous findings using the dot-probe task in a WS population (Dodd & Porter, 2010) and with other experimental studies reporting heightened social interest in happy faces (Haas et al., 2009). Second, we hypothesized that individuals with WS would display an attention bias to angry faces (compared to neutral). Although this prediction conflicted with Dodd & Porter's (2010) previous results in WS, we made this prediction based on the high rates of anxiety in WS coupled with the fact that anxiety is associated with threat biases in typically-developing individuals (Bar-Haim et al., 2007).

Beyond these group-based predictions, we were also interested in the impact of individual differences within the WS sample on patterns of attention bias to happy and angry faces. Specifically, we selected anxiety severity and IQ as potential moderators of attention bias patterns, given that individuals with WS show wide variation on both dimensions (Dodd & Porter, 2009). Specifically, we hypothesized that higher anxiety levels would be associated with a more prominent angry face bias, consistent with findings in anxious typically-developing populations (Bar-Haim et al., 2007). We did not expect anxiety to be associated with happy face biases. Regarding IQ, we could not make strong predictions on the impact of IQ on social dot-probe performance because, to our knowledge, there is not a previous literature on its effect in populations with developmental disorders or in typically-developing anxious or control populations. Thus, we considered an analysis of the potential moderating effects of IQ to be an important exploratory next step for social dot-probe research in WS and other developmental disorders. The over-arching goal of this study was to take a within-disorder approach to the study design in order to identify subgroups of individuals with WS who display attention biases to threat that may be amenable to cognitive modification.

Methods

Participants

Forty-six participants (13 males, 33 females) with WS completed an attention bias task and accompanying clinical, cognitive, and behavioral measures. Demographic data are shown in Table 1. All participants were recruited and tested at the Williams Syndrome Association (WSA) Family Convention (Boston MA, July 2012). Each subject had previously received the diagnosis of WS by genetic testing and/or an expert clinician. Testing sessions lasted

approximately 2 hours and participants received a \$20 gift card honorarium. Due to the cognitive demands of the testing, we restricted recruitment to individuals older than 12 years. Because of the complexities of obtaining informed consent in a sample with intellectual challenges and unique social features, such as a willingness to please, we obtained consent from a parent/guardian and consent/assent from the individual with WS. The study protocol was approved by the Massachusetts General Hospital Institutional Review Board.

Social dot-probe task

The social dot-probe task was identical to the one used by Dodd & Porter (2010). Full experimental details are provided in Supplementary Methods. In brief, a neutral face and an emotional face (happy or angry) from the same individual were presented simultaneously on the computer screen for 500 milliseconds (ms). Immediately after the faces disappeared, a dot appeared in the same location as either the neutral face (incongruent trials) or the emotional face (congruent trials). Participants were instructed to press a key as quickly as possible on the left or right side of the keyboard corresponding to the location of the dot. Accuracy and reaction time (RT) were recorded for all trials. The experiment consisted of 288 experimental trials divided into 12 blocks of 24 trials (8 happy/neutral, 8 angry/neutral, and 8 neutral/neutral trials).

The neutral/neutral trials were included to provide a baseline for reaction time when no emotion was present. This condition permits a distinction between engage and disengage effects (Koster, Crombez, Verschuere, & De Houwer, 2004). For example, a faster response to congruent trials may occur because the emotional image captures attention leading to vigilance on that side of the screen and therefore a faster response to congruent probes. Or, the participant might be slower during incongruent trials because they cannot disengage and shift attention from the emotional face to the opposite side of the screen. These two alternatives, which are not

mutually exclusive, can be tested by comparing reaction times in the congruent and incongruent conditions to the neutral/neutral condition, though it is important to note that inferences derived from this method continue to be debated in the literature (e.g. Mogg, Holmes, Garner, & Bradley, 2008).

Anxiety measurement

Because this study included a large age range of individuals with WS, we selected a parent-report measure of child anxiety, the Spence Children's Anxiety Scale (SCAS) (Nauta et al., 2004; Spence, 1998) that has been previously used with children, adolescents, and adults with WS (Dodd, Schniering, & Porter, 2009; Kirk, Hocking, Riby, & Cornish, 2013; Riby et al., 2014; Rodgers et al., 2012). In instances where items asked about school behaviors that were no longer relevant for adults, we instructed parents to consider alternative settings, such as day programs or work, consistent with previous studies (Dodd et al., 2009; Riby et al., 2014).

The SCAS consists of 38 items with an ordinal rating scale of never (0), sometimes (1), often (2), always (3). Six subfactors have been identified (see Table 1). The strong psychometric properties of the SCAS have been established for both clinical and research purposes (Nauta et al., 2004). Internal consistency of the total scale was excellent in the current study (cronbach's alpha =.91). A 10% missing item criterion was set in order for the questionnaire to be considered valid (2% of questionnaires failed). A total SCAS score of 24 has been suggested as an indicator of clinically significant anxiety based on the fact that it is one standard deviation about the mean in a community sample of typically-developing children (Nauta et al., 2004). This cut-off has been used previously in studies of anxiety in child and adult samples with WS (Kirk et al., 2013; Rodgers et al., 2012). Primary analyses will utilize

SCAS as a continuous measure, but follow-up categorical analyses will utilize the recommended cut-off of 24 to define cases with anxiety of clinical significance.

Cognitive Assessment

Kaufman Brief Intelligence Test – 2nd Edition (K-BIT2)

The Kaufman Brief Intelligence Test, 2nd edition (Kaufman & Kaufman, 2004) provides an estimate of verbal IQ, nonverbal IQ, and full-scale IQ. This test was administered by Ph.D. level researchers or trained research assistants.

Data Cleaning & Analysis

Data cleaning procedures for the social dot-probe task followed Dodd & Porter (2010), in accordance with previous work (Koster et al., 2004; Mogg, Philippot, & Bradley, 2004). Additional details are provided in Supplementary Methods. Analyses were performed with the cleaned mean reaction time (RT) data for each condition: happy congruent, happy incongruent, angry congruent, angry incongruent, and neutral. Bias scores for individual difference analyses were calculated by subtracting the congruent RT from the incongruent RT for happy and angry faces. Scores from the anxiety and cognitive measures were similarly inspected for outliers and normality. There were no extreme violations of normality and no outliers exceeding 3 standard deviations. Analyses were conducted with SPSS version 22.

Results

Demographics

Initial analyses examined the impact of several demographic variables on attention bias in the social dot-probe task to determine whether it was necessary to include these variables as covariates in subsequent analyses. Age, gender, and medication status were examined. There were no significant correlations between age and happy face bias ($r=.23, p=.12$) or angry face bias ($r=-.17, p=.27$) and no significant differences between the genders for happy ($t(44)<1, p=.91$) or angry face bias ($t(44)<1, p=.77$). Individuals taking medications with anxiolytic or stimulant effects did not significantly differ from those not taking these medications (all $ps >.18$). Thus, it was deemed unnecessary to include age, gender, or medication status as covariates in further analyses.

Repeated measures ANOVA & ANCOVA

A 2 (emotion: happy, angry) x 2 (congruency: congruent, incongruent) repeated-measures ANOVA was conducted where emotion and congruency were within-subjects factors (Table 2). Results showed a main effect of congruency, $F(1,45) = 9.66, p=.003$, while the main effect of emotion, $F(1,45)=1.59, p=.11$ and emotion x congruency interaction, $F(1,45)<1, ns$ were nonsignificant. These results indicated that, for the sample as a whole, there were significant biases toward both happy and angry faces, relative to neutral, but that this bias did not differ by emotion.

To further examine the impact of individual differences in IQ and anxiety severity on these attention bias patterns, we conducted a 2 (emotion: happy, angry) x 2 (congruency: congruent, incongruent) repeated measures ANCOVA. Emotion and congruency were both within-subjects factors as above, with verbal IQ and SCAS total anxiety score added as covariates. Both covariates were mean-centered according to recommendations for repeated-

measures ANCOVA (Delaney & Maxwell, 1981; Thomas et al., 2009). We selected verbal IQ as the primary index of cognitive functioning because it is a strength for individuals with WS, but results were comparable when nonverbal IQ was covaried (data not shown). Because within-subjects effects are independent of covariates (i.e., the same individual has the same IQ/anxiety severity measure across conditions of the experiment), the within-subjects effects of the previous repeated-measures ANOVA were similar to this analysis, differing only because of a few individuals with missing data: congruency, $F(1, 42) = 8.23, p = .006$, emotion, $F(1, 42) = 2.34, p = .13$, emotion x congruency, $F(1, 42) < 1, ns$. The between-subjects effects of the covariates were not significant: verbal IQ, $F(1, 42) = 1.90, p = .18$, SCAS anxiety total, $F(1, 42) < 1, ns$. Importantly, both verbal IQ and SCAS total anxiety score contributed to significant higher-order interactions that provided a context for interpreting all other main effects and interactions in the full model: verbal IQ x emotion x congruency, $F(1, 42) = 10.32, p = .003$, SCAS anxiety total x emotion x congruency, $F(1, 42) = 5.60, p = .023$. None of the other two-way interactions between the covariates and within-subjects factors reached significance (all p 's $> .1$). These three-way interactions suggested that the influence of emotion on face bias differed significantly as a function of IQ and anxiety, patterns that required further analysis. We decomposed the 3-way interactions separately, first examining verbal IQ and then anxiety.

IQ x emotion x congruency interaction

To understand the verbal IQ x emotion x congruency interaction, we used a median split at verbal IQ=77 to define a lower verbal IQ ($N=25, M=70, SD=6.4$, range 52-77) and higher verbal IQ group ($N=21, M=85, SD=5.9$, range 78-97) (Table 3). The median split strategy was chosen because it resulted in roughly equal sample sizes. We note non-significant trends in these

analyses as they are conducted in smaller subsamples to clarify the significant 3-way interaction. Figure 1 illustrates that the emotion x congruency interaction is in opposite directions in the two IQ groups, resulting in the significant 3-way interaction (lower IQ group emotion x congruency interaction, $F(1,24)=4.15, p=.053$, higher IQ group emotion x congruency interaction, $F(1, 20)=3.39, p=.081$). The cross-over nature of this interaction explained why the overall emotion x congruency interaction was not significant in the full sample. One-sample t-tests (compared to a reference of 0) further confirmed the overall pattern: in the low verbal IQ group, the happy face bias was significantly different from zero, $t(24) = 2.70, p=.013$, but the angry face bias was not, $t(24) < 1, p=.41$. In the high verbal IQ group, the opposite pattern was evident where the angry face bias was significantly different from zero, $t(20) = 2.76, p=.012$, but the happy face bias was not, $t(24) < 1, p=.50$. Overall, results showed that as verbal IQ increased, the angry face bias increased ($r=.41, p=.005$) and the happy face bias diminished ($r=-.33, p=.03$) (Table 5), which was the pattern responsible for the significant 3-way verbal IQ x emotion x congruency interaction.

Anxiety x emotion x congruency interaction

To understand the SCAS total anxiety x emotion x congruency interaction, we split the sample using the clinical cut-off on the SCAS of 24 to define a lower anxiety group ($N=28, M=13.6, SD=5.5, \text{range } 4-22$) and a higher anxiety group ($N=17, M=32.8, SD=8.0, \text{range } 25-55$) (Table 4). We note non-significant trends in these analyses as they are conducted in smaller subsamples to clarify the significant 3-way interaction. Similar to Figure 1, Figure 2 shows an opposite emotion x congruency interaction in the two anxiety groups, which resulted in the significant 3-way interaction (lower anxiety group emotion x congruency interaction,

$F(1,27)=6.15, p=.02$, higher anxiety group emotion x congruency interaction, $F(1,16)=3.49, p=.08$). The cross-over nature of this interaction explained why the emotion x congruency interaction was not significant in the full sample. One-sample t-tests (compared to a reference of 0) further confirmed the overall pattern: in the lower anxiety group ($SCAS \leq 24$), the happy face bias was significantly different from zero, $t(27)=2.93, p=.007$, but the angry face bias was not, $t(27)<1, p=.44$. In the higher anxiety group ($SCAS > 24$), the opposite pattern was evident where the angry face bias was significantly different from zero, $t(16)=2.54, p=.022$, but the happy face bias was not, $t(16)<1, p=.89$. Overall, results showed that as SCAS total anxiety symptoms increased, there were nonsignificant trends for the angry face bias to increase ($r=.28, p=.059$) and the happy face bias to decrease ($r=-.23, p=.13$) (Table 5), a pattern which resulted in the significant 3-way anxiety x emotion x congruency interaction.

The similarity of the patterns in Figure 1 and 2 raises the question of whether the IQ and anxiety interactions were independent. We therefore examined the independence of these two effects. First, verbal IQ and anxiety were not significantly correlated, $r=.09, p=.56$. Second, we note that the 3-way interactions accounted for unique variance as they were both significant when entered into the same model. Thus, the independence of these effects indicates that individuals with higher IQs *and* higher anxiety can be expected to show the largest angry face bias.

Anxiety subtypes analysis

To further examine the differing patterns of attention bias according to anxiety levels, we examined correlations between happy and angry face bias and SCAS subscale scores (Table 5).

We observed that the correlation between SCAS total anxiety and the angry face bias was

primarily driven by the SCAS generalized anxiety scale (GAD), albeit at a trend-level ($r=.28$, $p=.059$). In contrast, the correlation between SCAS total anxiety and the happy face bias was primarily driven by the SCAS social anxiety subscale, again at a trend-level ($r=-.28$, $p=.064$).

Engage/Disengage Effects

An engage effect is defined as a faster reaction time for emotional (happy or angry) *congruent* (probe is in the same location as the emotional face) trials compared to neutral-neutral trials. In contrast, a disengage effect is defined as slower reaction times for emotional *incongruent* (probe is in the location of the neutral face) trials compared to neutral-neutral trials. We tested whether the happy face bias in the lower IQ group and lower anxiety groups and the angry face bias in the higher IQ and higher anxiety groups were attributable to engage and/or disengage effects by comparing the condition means to the neutral condition via paired-sample t -tests.

In all cases, the pattern was consistent in suggesting a possible disengage effect. For the happy face bias in the lower IQ group, there was a trend indicating participants were slower in the happy incongruent trials $t(24)=2.03$, $p=.054$, but not faster in the happy congruent trials, $t(24)=1.26$, $p=.22$, compared to the neutral trials. For the angry face bias in the higher IQ group, there was a trend indicating that participants were slower in the angry incongruent trials, $t(20)=2.01$, $p=.058$, but not faster in the angry congruent trials, $t(20)=1.65$, $p=.12$ (though note the near-trend), as compared to the neutral trials.

For the happy face bias in the lower anxiety group, participants were slower in the happy incongruent trials $t(27)=2.10$, $p=.045$, but not faster in the happy congruent trials, $t(27)=1.60$, $p=.12$, compared to the neutral trials. Similarly, for the angry face bias in the higher anxiety

group, participants were slower in the angry incongruent trials, $t(16)=2.55, p=.022$, but not faster in the angry congruent trials, $t(16)=1.10, p=.29$, as compared to the neutral trials. Taken together, these results provide trend-level evidence that face bias effects in WS, regardless of emotion, are most consistent with difficulties shifting away from the emotion than attentional capture effects.

Discussion

The current study is the largest attention bias study in WS, to date. Results showed a significant impact of verbal IQ and anxiety levels on attention bias to emotional faces. Individuals with lower verbal IQ ($M=70, SD=6.4$) and lower SCAS total anxiety scores ($M=13.6, SD=5.5$) showed a statistically significant bias toward happy faces, but not angry faces. In contrast, individuals with higher verbal IQ ($M=85, SD=5.9$) and higher SCAS total anxiety scores ($M=32.8, SD=8.0$) showed the reverse pattern; a bias toward angry faces, but not happy faces. In other words, as IQ and anxiety increased, the angry face bias increased and the happy face bias decreased in this WS sample. There was a consistent pattern, albeit at mostly trend-levels, indicating that face bias effects in WS, regardless of emotion, were most consistent with disengagement effects from the emotional face rather than attentional capture. Overall, these results provide the first evidence that IQ and anxiety levels moderate attention bias effects to faces in WS. In the following, we discuss the research and clinical implications of these findings for the anxiety phenotype in WS.

We hypothesized that individuals with WS would show both a happy and angry face bias, the former hypothesis based on previous findings with the social dot-probe task in WS (Dodd & Porter, 2010) and the latter hypothesis based on high rates of anxiety in WS, particularly GAD

which is associated with threat face biases in typically-developing populations. In the full sample, these hypotheses were supported, as there was a significant congruency effect but no emotion x congruency interaction, indicating that there were significant happy and angry face biases in this sample that did not differ by emotion. However, further analysis of our data considering possible moderating effects of anxiety and IQ showed that the patterns of emotional face biases were more complex than we had predicted. First, we found that higher anxiety was associated with a larger angry face bias, which we predicted based on findings of attention bias in anxious typically-developing populations (Bar-Haim et al., 2007). However, we also found that higher anxiety was associated with a diminished happy face bias, which was not an effect we had predicted. The analyses examining IQ as a moderator of the happy and angry face bias were exploratory and revealed potentially important findings that are discussed further below. Taken together, the impact of individual differences in anxiety and IQ on emotional face bias patterns were more complex than we hypothesized and therefore require further examination and replication in independent samples.

Only one previous study has examined attention bias to emotional faces in WS (Dodd & Porter, 2010). Their results showed a significant happy face bias which was larger in scale than both their mental and chronological age matched controls. In contrast, the WS individuals in their study did not show a significant angry face bias, which was consistent with similar null effects in both their control groups (Dodd & Porter, 2010). On the surface, the fact that Dodd & Porter (2010) did not detect an angry face bias appears inconsistent with the current results, but sampling differences appear to resolve the discrepancy. Specifically, the Dodd & Porter (2010) study included a sample of individuals with WS (full-scale IQ range 53-77) who were most comparable to the lower IQ group in the current study (verbal IQ range 52-77). When these two

sets of results are compared, there is good convergence with direct replication of the face bias effects - a significant happy but not angry face bias. In fact, the reaction times and the magnitude of the biases are quite comparable between the studies, demonstrating excellent consistency for the lower IQ portion of our cohort that is most comparable to Dodd & Porter's (2010) sample.

Given that attention bias to threat is a necessary precondition for therapeutic approaches attempting to modify this bias, these results indicate that attention bias modification may be most appropriate for individuals with WS with relatively high IQ and clinically significant anxiety symptoms. These two effects of IQ and anxiety were independent so these results indicate that individuals with high IQ *and* clinically significant anxiety would be expected to have the strongest angry face bias (in this sample $N=8$, $M=31.8$, $SE=12.8$ ms). As reviewed previously, such attention bias modification trials have shown some promise in typically-developing individuals with anxiety disorders (i.e., Clarke et al., 2014), though debate remains (i.e., Emmelkamp, 2012). Such attention bias modification protocols have not yet been tested in individuals with WS, nor, to our knowledge, in any populations with developmental disorders. The current results point to the potential utility of an attention bias modification trial in individuals with WS who have high anxiety levels (SCAS total score >24) and high IQ (i.e., verbal IQ above the intellectual disability range). The finding that the happy face bias was diminished in the anxious, higher IQ sample and negatively correlated with anxiety points to the potential utility of attention bias modification toward happy faces in individuals with WS (i.e., Waters, Pittaway, Mogg, Bradley, & Pine, 2013), rather than the more common approach of training toward neutral faces (Bar-Haim, 2010). More generally, given high rates of anxiety disorders in populations with developmental disorders (Reardon, Gray, & Melvin, 2015),

attention bias and attention bias modification warrant further exploration in these populations taking into account key moderators such as IQ.

The reason for the different patterns of angry and happy face bias across IQ remains unclear. In other developmental disorders, such as autism spectrum disorder, children with higher IQ are at higher risk for anxiety (Sukhodolsky et al., 2008; S. W. White, Oswald, Ollendick, & Scahill, 2009). The typical interpretation of this finding is that individuals with higher IQ are more aware of their challenges and threatening situations in the environment and this sensitivity may manifest in anxiety. Such an interpretation would be broadly consistent with the findings reported in the current study that higher IQ individuals with WS showed a larger angry face bias and this bias was modestly correlated with anxiety. Although there was not a direct correlation between anxiety and verbal or nonverbal IQ in this sample ($r=.09$, $r=.12$, respectively Table 5), a previous study with a larger sample of individuals with WS ($N=59$) did find a significant relationship between increased anxiety and IQ ($r=.27$), albeit with different measures of both constructs (Beck Anxiety Inventory and Wechsler IQ scales WAIS-R/III or WASI) (Ng, Järvinen, & Bellugi, 2014). Although the correlations between anxiety and IQ in our sample and this previous study seem quite disparate, because of the relatively small samples, the 95% confidence interval of our correlation between verbal IQ and SCAS total anxiety ranges from $r= -.19 - .35$ and encompasses the estimated obtained by Ng et al. (2014). As such, our failure to detect a relationship between IQ and anxiety may be attributable to measurement and/or sampling differences.

Our results, in concert with Dodd & Porter (2010) support disengage effects rather than engage effects as an explanation for attention bias to emotional faces, although both sets of results report largely trend-level findings. However, it is important to qualify this interpretation

by noting that the experimental methods to distinguish engage vs. disengage effects in the dot-probe task have been recently called into question (Mogg et al., 2008). The main issue is that the dot-probe paradigm cannot distinguish a disengage effect from a general motor slowing effect due to threat. Mogg and colleagues (2008) demonstrated that accounting for this general slowing effect with a separate experimental task resulted in a complete reversal of the data interpretation from a disengagement effect to an engage effect. As a result, we note that the raw data in our experiment are consistent with a disengage effect, but we offer this interpretation cautiously because we could not control for general slowing effects due to threat. Nevertheless, similar findings consistent with a disengage effect have been found in other experimental paradigms, most notably eye tracking experiments showing prolonged gaze at faces, particularly the eyes of a face (e.g., Porter, Shaw, & Marsh, 2010; Riby & Hancock, 2008). Possible disengagement difficulties are also consistent with more general executive dysfunction reported in WS (Menghini, Addona, Costanzo, & Vicari, 2010; Rhodes, Riby, Park, Fraser, & Campbell, 2010), and raise interesting questions about the relationship between executive functioning and anxiety in WS. In typically developing children, such executive functions are reported to moderate the association between an anxious temperament and the development of an anxiety disorder (Fox, 2010). Such developmental processes may also be relevant for individuals with WS and may guide prevention and intervention approaches for anxiety.

These results should be considered in relation to the functional imaging studies in WS using threat and happy faces (Haas & Reiss, 2012). One consistent finding is a difference in amygdala response in which individuals with WS show increased activation to happy faces, but diminished activation to threat faces, compared to controls (Haas et al., 2009; Meyer-Lindenberg et al., 2005). Neuroimaging studies of WS have typically included higher functioning

individuals with WS because of the cognitive demands of participating in a functional imaging experiment. Thus, these samples are most comparable to the high end of our IQ distribution. Comparing these results leads to an apparent inconsistency. Why would this higher IQ group show diminished amygdala activation to threatening faces while simultaneously showing an angry bias in our task related to difficulties disengaging from the angry face? Beyond the usual difficulties in reconciling behavioral and imaging results, such as task and sample differences, a recent study by Kirk et al. (2013) adds a possible explanation. These authors showed that individual differences in anxiety in WS influenced fixation on the face such that anxious individuals were more likely to allocate attention away from the eye region. It is possible that this strategy may downregulate amygdala activation yet still lead to an angry bias group effect, consistent with a “vigilance-avoidance” pattern of attention bias where an initial orientation to threat may be followed by avoidance strategies (Mogg & Bradley, 1998). Further work that integrates a multi-measure approach (i.e., Kirk et al., 2013; Plesa Skwerer et al., 2011), including attention bias paradigms, fMRI, and eye tracking would be necessary to resolve these questions in WS.

The current findings should be considered in light of some additional limitations. First, we chose a within-subject design focused on attention bias in WS because we were specifically interested in anxiety treatment approaches in WS. In our clinical experience, the psychiatric needs of individuals with WS are vastly under-served, with anxiety as one of the primary referral concerns. Nevertheless, our within-subjects design means that we cannot directly compare the magnitude of the happy or angry face bias in WS to directly matched mental age or chronological age controls. Instead, our research design focused on identifying subgroups of

individuals with WS who might be most likely to benefit from attention bias modification trials to treat severe anxiety symptoms.

Second, we relied on parent-report of anxiety in WS, which tends to under-estimate anxiety according to previous studies (Dykens, 2003; Stinton et al., 2010, 2012). Although we attempted to collect the self-report of the WS individuals using the SCAS, we found that even with visual supports, there was too much confusion regarding the questionnaire anchors for the data to be used in analyses. Despite the absence of self-report data, previous studies have found a strong correlation between self- and caregiver-report ($r=.78$, Stinton et al., 2012) suggesting that caregiver-report does capture reliable variance in anxiety.

Third, we selected the social dot-probe task, rather than a non-social dot-probe, because of the larger previous literature on the social task and the inherent interest individuals with WS have in faces. Nevertheless, it remains a possibility that threatening scenes may be a better training paradigm for attention bias modification in WS, perhaps especially for specific phobias.

Finally, there is a mixed literature regarding the psychometric properties of the dot-probe task (Brown et al., 2013; Schmukle, 2005; Staugaard, 2009). This literature suggests that group analyses, rather than individual difference analyses, are preferable for social dot-probe experiments because the former require less stringent psychometric properties. In line with this approach, our primary analysis utilized a grouping strategy (i.e., repeated measures ANOVA and ANCOVA). The fact that we replicated previous results (Dodd & Porter, 2010) using this group design provides additional assurance of the validity of the results. However, because we were interested in individual differences in anxiety and IQ, we also report effects of these covariates on attention biases. In such an analysis, increased task error variance will diminish power to detect significant relationships, making false negatives more of a concern than false positives.

Thus, we note trend-level findings to guide future work but acknowledge the need for replication.

In conclusion, these results enhance our understanding of basic attentional mechanisms that influence the viewing of emotional faces by individuals with WS. To our knowledge, this is the first report of a significant moderating effect of IQ on attention bias, potentially making the results relevant for other developmental disorders beyond WS. We report complex interactions in which increasing IQ and anxiety levels are associated with a decreased happy face bias and an increased angry face bias. If replicated, these results suggest that attention bias modification protocols to improve anxiety symptoms in WS may be most effectively targeted to anxious individuals with WS with relatively high IQ.

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Figure Captions

Figure 1. Angry and happy face bias plotted based on a median split by Verbal IQ. Means and standard errors (error bars) are plotted. *P*-values indicate means that are significantly different from 0.

Figure 2. Angry and happy face bias plotted based on clinical anxiety cut-offs on the Spence Children's Anxiety Scale (SCAS) (parent-report). Means and standard errors (error bars) are plotted. *P*-values indicate means that are significantly different from 0.

Figure 1.

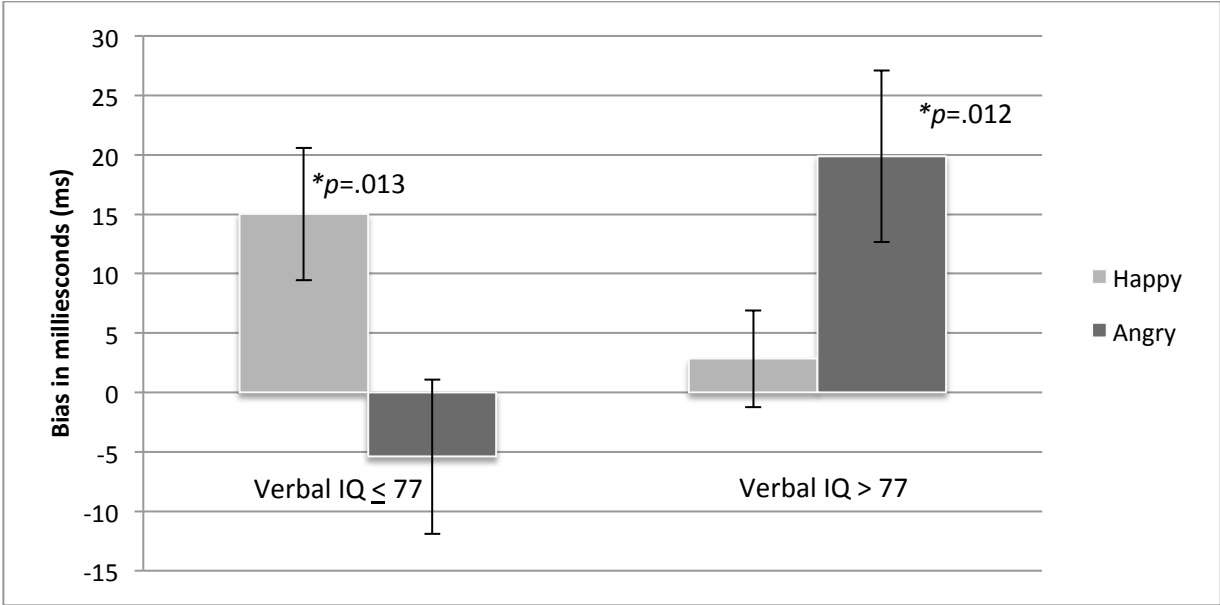


Figure 2.

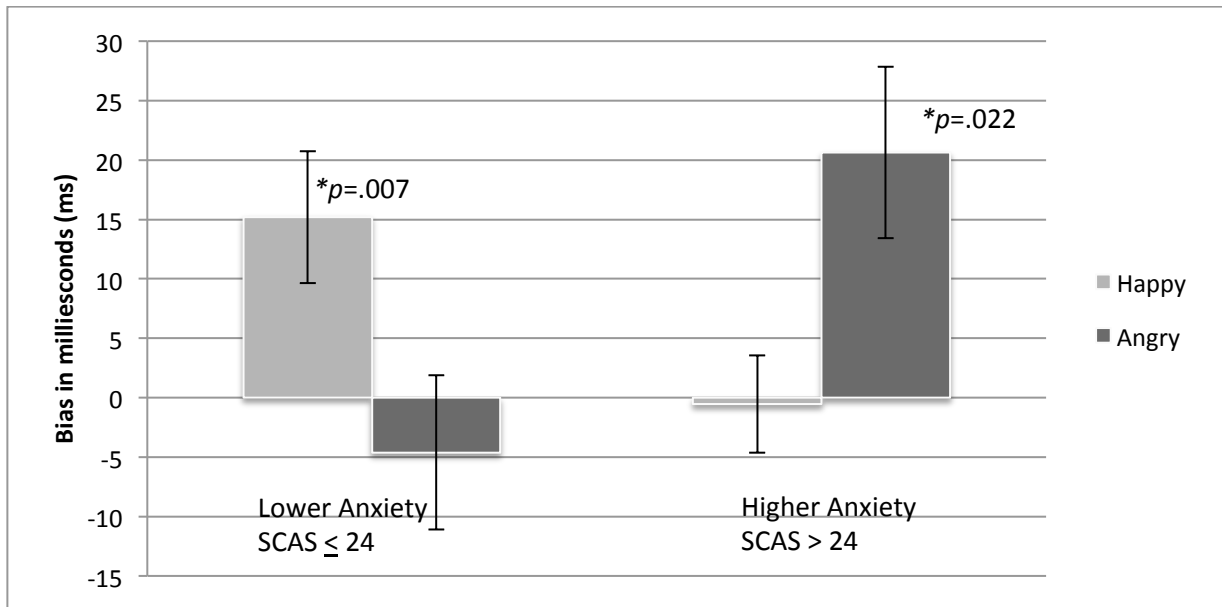


Table 1. Demographics for Williams syndrome sample.

	<i>M (SD)</i>	<i>Range</i>
Age (years)	26.8 (10.4)	12.5-56.5
Verbal IQ	77.0 (9.8)	52-97
Nonverbal IQ	72.9 (17.1)	40-97
Composite IQ	71.8 (12.1)	47-95
SCAS Children’s Anxiety Scale (Parent-report)	20.9 (11.4)	4-55
SCAS social phobia	3.7 (2.9)	0-12
SCAS generalized	5.7 (2.9)	1-13
SCAS separation	3.2 (3.0)	0-13
SCAS panic	2.6 (2.5)	0-11
SCAS physical injury	4.2 (2.4)	0-10
SCAS OCD	1.5 (1.8)	0-9
SCAS clinical cut-offs	<i>N</i>	<i>Percent</i>
Clinical case status (SCAS > 24)	17	38%
Medication status	<i>N</i>	<i>Percent</i>
Med with anxiolytic effects	19	41.3
Med with stimulant effects	4	8.7

Table 2. Mean reaction times (ms) for the social dot-probe conditions in the full sample.

Condition	Full Sample <i>M (SD)</i> <i>N=46</i>
Angry Congruent	607.42 (115.83)

Angry Incongruent	614.61 (107.37)
Happy Congruent	601.61 (104.52)
Happy Incongruent	612.34 (114.03)
Neutral	605.44 (109.27)

Table 3. Mean reaction times (ms) for the social dot-probe conditions based on a median split of verbal IQ.

Condition	VIQ \leq 77	VIQ $>$ 77
	<i>M (SD)</i> <i>N=25</i>	<i>M (SD)</i> <i>N=21</i>
Angry Congruent	632.18 (130.33)	577.95 (90.15)
Angry Incongruent	626.99 (112.38)	599.87 (101.80)
Happy Congruent	613.71 (114.01)	587.20 (92.62)
Happy Incongruent	630.38 (125.39)	590.86 (97.45)
Neutral	620.55 (118.73)	587.45 (96.56)

Table 4. Mean reaction times (ms) for the social dot-probe conditions based on a clinical cut-off on the Spence Children’s Anxiety Scale (SCAS).

Condition	SCAS \leq 24	SCAS $>$ 24
	<i>M (SD)</i> <i>N=28</i>	<i>M (SD)</i> <i>N=17</i>
Angry Congruent	632.91 (120.86)	577.24 (92.02)
Angry Incongruent	628.26 (109.64)	600.78 (101.27)
Happy Congruent	616.18 (107.76)	588.49 (91.85)
Happy Incongruent	633.46 (119.08)	587.94 (96.32)
Neutral	623.83 (112.47)	585.16 (96.96)

Table 5. Correlations between attention bias and SCAS anxiety scales.

	Happy bias	Angry bias	Verbal IQ	Nonverbal IQ
Happy bias	--	-.27†	-.33*	-.10
Angry bias	-.27†	--	.41**	.33*
SCAS total	-.23	.28†	.09	.12
SCAS social phobia	-.28†	.23	.19	.15
SCAS generalized	-.17	.28†	.08	.19
SCAS separation	-.23	.22	.15	.10
SCAS panic	-.11	.20	-.02	.03
SCAS physical injury	-.09	.11	-.10	-.05
SCAS OCD	-.10	.23	.06	.12
Verbal IQ	-.33*	.41**	--	.29*
Nonverbal IQ	-.10	.33*	.29*	--

*p<.05, **p<.01, †p<.1

