Title: There's that scary picture: attention bias to threatening scenes in Williams syndrome

Running Head: Attention Bias in WS

Authors: Helen F. Dodd[1] and Melanie A. Porter[2]

[1]Macquarie Centre for Cognitive Science, Macquarie University, Marsfield, NSW 2109, Australia. Email: helen.dodd@mq.edu.au. Telephone: +61 (0)2 9850 4866. Fax: +61 (0)2 9850 8062[a]

[2]Department of Psychology, Macquarie University, Marsfield, NSW 2109, Australia. Email: melanie.porter@mq.edu.au

Corresponding author: Helen F. Dodd

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[a] Present address and affiliation: Centre for Emotional Health, Department of Psychology, Macquarie University, Marsfield, NSW 2109, Australia. Email remains the same.

Abstract

There is increasing evidence that Williams syndrome (WS) is associated with elevated anxiety that is non-social in nature, including generalised anxiety and fears. To date very little research has examined the cognitive processes associated with this anxiety. In the present research, attentional bias for non-social threatening images in WS was examined using a dot-probe paradigm. Participants were 16 individuals with WS aged between 13 and 34 years and two groups of typically developing controls matched to the WS group on chronological age and attentional control ability respectively. The WS group exhibited a significant attention bias towards threatening images. In contrast, no bias was found for group matched on attentional control and a slight bias away from threat was found in the chronological age matched group. The results are contrasted with recent findings suggesting that individuals with WS do not show an attention bias for threatening faces and discussed in relation to neuroimaging research showing elevated amygdala activation in response to threatening non-social scenes in WS.

1.1

Williams syndrome (WS) is a rare genetic disorder caused by a microdeletion of approximately 28 genes on one copy of chromosome 7 (Ewart et al., 1993). WS is associated with a mild to moderate intellectual impairment, facial dysmorphology, medical complications and an outgoing, hyper-social personality (Bellugi, Lichtenberger, Jones, Lai, & St, 2000; Einfeld, Tonge, & Florio, 1997; Mervis & Klein-Tasman, 2000). In striking contrast to this fearless social behaviour, individuals with WS experience significant anxiety that is 'non-social in nature' (Jarvinen-Pasley et al., 2008, p.7). Recent research has begun to delineate the neural and cognitive processes that underpin this dissociation between social and non-social anxiety in WS (Dodd & Porter, in press; Meyer-Lindenberg et al., 2005; Munoz et al., 2010). However, the majority of research has remained focused on WS social behaviour (Haas, Mills, Yam, Hoeft, Bellugi, & Reiss ,2009; Santos, Silva, Rosset, & Deruelle, 2010; Martens, Wilson, Dudgeon, & Reutens, 2009) and only a small body of research has examined cognitive processes associated with non-social anxiety in this population. The present research aims to address this gap in the literature by examining attentional processing associated with elevated non-social anxiety in WS.

Early indications that WS was associated with high levels of anxiety, fears and worries came from questionnaire measures of psychopathology (e.g. Einfeld et al., 1997; Udwin, 1990). These observations have since been supported by studies using diagnostic interviews validated against the Diagnostic and Statistical Manual for Mental Disorders (DSM; American Psychiatric Association, 1994). For example, in the most comprehensive assessment of clinical anxiety in WS conducted to date, Leyfer, Woodruff-Borden, Klein-Tasman, Fricke, and Mervis (2006) assessed 119 children with WS and found that rates of GAD (12%) and Specific Phobia (54%) were

unusually high relative to the typically developing population. Similar prevalence rates have also been found in samples of adults with WS (Dodd & Porter, 2009; Dykens, 2003). Interestingly, however, there is little evidence that rates of Social Phobia are elevated in this population; prevalence rates and levels of anxiety symptoms tend to be consistent or lower than those reported in typically developing groups (Dodd & Porter, 2009; Dodd, Schniering & Porter, 2009; Leyfer et al., 2006).

In an influential study, Meyer-Lindenberg et al. (2005) found that patterns of amygdala activation in WS were highly consistent with this pattern of dissociated social and non-social anxiety; relative to typically developing controls, individuals with WS exhibited *elevated* amygdala activation in response to threatening non-social stimuli and *attenuated* amygdala activation in response to threatening social stimuli. Further analyses revealed abnormalities in the prefrontal system involved in down-regulation of the amygdala in the WS participants. These findings, recently replicated (Munoz et al., 2010), provided initial insight into the neurological processes that may underpin the dissociation between social and non-social anxiety in WS. Subsequent research has extended these findings and demonstrated that, although individuals with WS exhibit attenuated amygdala activation in response to fearful faces, elevated amygdala activation, relative to typically-developing controls, is found in response to happy faces (Haas et al., 2009).

Both the amygdala and the prefrontal cortex (PFC) have been implicated in cognitive models of attention in anxiety (Mathews & Mackintosh, 1998; Bishop, 2007). Building on biased competition models of selective attention these models propose that when multiple stimuli compete for attention, the outcome depends upon the interaction of bottom-up threat detection mechanisms and top-down control mechanisms. These competing inputs are thought

to be underpinned by the amygdala and the PFC respectively. That is, the amygdala is theorised to support the early threat-detection mechanism and the initial orienting of attention and the PFC thought to underpin the control of attentional resources required to inhibit further processing of selected stimuli (Bishop, 2007, 2009; Cisler & Koster, 2010; Pine, 2007). It seems plausible, therefore, that the pattern of amygdala and PFC activation observed in WS might indicate atypical attentional deployment to certain stimuli. Two recent studies have found initial support for this hypothesis. Dodd and Porter (2010) used a dot-probe paradigm (described below) and found that individuals with WS were biased to attend to happy faces but not to angry faces and Santos et al. (2010) found decreased detection of angry faces in WS using a visual search task compared to typically developing individuals. Both of these findings are consistent with the patterns of amygdala activation reported for social stimuli, outlined above (Meyer-Lindenberg et al., 2005; Haas et al., 2009). To date, however, there is no comparable research examining attentional processing related to non-social stimuli in WS. If the patterns of amygdala activation found in previous research are genuinely associated with abnormalities in attentional deployment in WS, an attention bias for images depicting non-social threat would also be expected. The present research addresses this hypothesis using a dot-probe task based on that used by Dodd and Porter (2010).

The dot-probe task is one of the most commonly used paradigms for assessing attention bias (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007). In the dot-probe task, a neutral stimulus and a threatening stimulus are presented simultaneously, followed immediately by a probe in the same location as either the threatening or neutral stimulus. Participants are instructed to respond to the probe as quickly as possible. This paradigm has been used to assess both within-subjects and between-subjects attention biases.

A within-subjects bias is found when a group responds significantly faster to the probe when it follows the threatening stimulus (congruent trial) than the neutral stimulus (incongruent trial). A between-subject bias occurs when significant differences in the size of the bias (congruent trials – incongruent trials) are found between two or more groups. Both types of bias are consistently found in anxious typically developing adults and children (Bar-Haim et al., 2007).

Although the dot-probe task has been used extensively to examine threat-related attention bias in anxious populations, there has been some debate regarding which components of attention the task measures. Derryberry and Reed (2002) highlighted that a faster response time on congruent than incongruent trials could occur for two reasons: because the threat image captures attention, which leads to a faster response time on congruent trials or, alternatively, because it is difficult to disengage attention from the threat image, which leads to a slower response time on incongruent trials. Koster, Crombez, Verschuere and De Houwer (2004) explored these alternatives by including a baseline condition in which both images were neutral. By comparing congruent and incongruent trials to the neutral condition it was possible to differentiate between vigilance and disengage effects. Using this procedure, Koster et al. (2004) found that attention bias is primarily driven by disengage effects rather than enhanced vigilance for threat. Other research that has investigated vigilance and disengage effects has supported these findings (Salemink, van den Hout, & Kindt, 2007; Yiend & Mathews, 2001).

1.2. Aims and Hypotheses

The aim of the present research was to examine whether individuals with WS exhibit an attention bias for non-social threat using a dot-probe task. In light of evidence that individuals with WS are at increased risk for GAD and Specific Phobia (Dodd & Porter, 2009; Dykens, 2003;

Leyfer et al., 2006) and that individuals with WS exhibit elevated amygdala activation in response to threatening non-social stimuli (Meyer-Lindenberg et al., 2005; Munoz et al., 2010), it was hypothesised that the WS group would exhibit a significant within-subjects bias towards threatening stimuli and that the overall bias found in the WS group would be significantly larger than any bias exhibited by typically developing controls matched on attentional control or chronological age (between-subjects bias).

A neutral condition, in which two neutral images were presented, was included such that vigilance and disengage effects could be examined. Given previous findings that attention bias is primarily driven by difficulties disengaging from threat, it was hypothesised that any attention bias found in the WS group would be due to disengage effects rather than vigilance.

To examine whether any attention bias found was related to current anxiety in the WS group, the analyses were conducted with and without anxiety symptoms entered as a covariate and the overall bias was compared between WS participants who met criteria for a current anxiety diagnosis and those who did not.

Method

2.1 Participants

The study involved 48 participants including 16 participants with WS, 16 typically developing participants individually matched to the WS group on attentional control and 16 typically developing participants individually matched to the chronological age of the WS group. Demographic data for each group is shown in Table 1.

2.1.1 Williams syndrome group.

Participants were sixteen individuals with WS (N=16, 9 male) aged between 13 and 34 years with a mean aged of 21.04 years. All participants had received a diagnosis of WS following a positive florescent in situ hybridization (FISH) test showing deletion of the elastin gene at 7q11.23 (Fryssira et al., 1997) and exhibited the typical WS phenotype. Participants were recruited through the Australian Williams Syndrome Association. Due to the attentional demands of the task, only individuals with a mild to moderate intellectual impairment who had a mental age of at least 6.5 years as assessed using the Woodcock-Johnson Test of Cognitive Ability – Revised (WJ-COG-R; Woodcock & Johnson, 1989, 1990) were invited to participate. The mental age of the participants with WS ranged from 6.75 years to 10.58 years, with a mean of 8.09. The standard scores for general cognitive functioning ranged from 48 to 77, with a mean of 64..

Current diagnostic status, according to DSM-IV criteria, was assessed through an interview with the primary caregiver using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman, Birmaher, Brent, Rao, & et al., 1997). Seven of the WS participants met criteria for at least one anxiety disorder, six met criteria for a Specific Phobia and one met criteria for Generalised Anxiety Disorder.

2.1.2 Chronological age comparison group (CA).

Sixteen typically developing individuals individually matched to the WS group on chronological age, t (15) =-0.023, p = 0.982, were recruited via a university-administered register of teenagers and young adults who are interested in participating in research. The inclusion of a

chronological age matched control group allows any influences of chronological age on attention bias to be assessed. This is necessary because the WS participants were markedly older than the participants in the attentional control comparison group (see table 1).

2.1.3 Attentional control comparison group (AC).

Sixteen typically developing children were recruited through privately funded primary schools in the Sydney area. As performance on the dot-probe task may be affected by attentional control, in particular inhibition of prepotent responses and controlled disengagement of attention (Derryberry & Reed, 2002; Kindt, Bierman, & Brosschot, 1997), these control participants were matched to the WS participants according to performance on The Shape School Test (Espy, 1997). The Shape School Test uses a storybook design to assess inhibition, or response suppression, and switching, or context controlled selection (Espy, 1997). This task has good internal consistency and external validity (Esby, Bull, Martin, & Stroop, 2006) and has been used successfully in previous WS research (Porter, Coltheart and Langdon, 2007). The combined measure of attentional control is calculated based on participants' performance on a naming task in which they have to name only those characters who meet condition A (inhibition / response suppression) and choose their name based on rule B (switching / context controlled selection). An overall attentional control score is calculated by dividing the accuracy score (i.e. the number of characters named correctly) by the time taken to complete the task. The AC and WS groups were matched on this score, t (16) 1.05, p = 0.310, mean scores are shown in Table 1.

To select these participants, a sample of typically developing children whose chronological age matched the mental ages of the WS participants completed the Shape School

task. Participants were then selected from this group on the basis of their Shape School scores. The chronological age of the AC group is therefore equivalent to the mental age of the WS group (see table 1).

All control participants were considered to be typically-developing by their teachers and their parents. Children with a developmental disorder, clinical diagnosis, or any history of atypical development were not selected to participate.

2.2. Design

The dot-probe task was based on that used in previous studies (e.g. Dodd & Porter, 2010; Waters, Lipp, & Spence, 2004) and included 240 experimental trials divided into eight blocks of thirty trials. Each block incorporated twenty critical trials in which a neutral image and a threat image were presented. Threat position and probe position were manipulated such that each block included ten *congruent* trials and ten *incongruent* trials. A congruent trial was defined as a trial in which the threat image cued the spatial location of the probe. The position of the threat and probe were counterbalanced within conditions. In addition to the twenty critical trials, each block also comprised ten neutral trials, in which two neutral images were presented. Neutral trials were included to provide a baseline for participants' reaction time when no threat was present. On these trials the position of the probe was also counterbalanced. This design was replicated across the eight blocks. The images were rotated such that each image was displayed once in each block and each image pairing was only seen once throughout the experiment. Trials were randomized within blocks for each participant.

2.3 Materials

2.3.1 Dot-probe task.

Twenty 'threat' images and forty 'neutral' images were selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2005), a set of colour pictures with normative ratings for valence, dominance and arousal[1]. The IAPS images have been used previously in dot-probe attention bias experiments (e.g. Koster et al., 2004; Waters et al., 2004) and also in research with WS (Meyer-Lindenberg et al., 2005). Images were chosen that represented environmental or 'non-social' threat, such as animals (dogs, spiders etc.), disasters (storms, sinking ships etc) and medical procedures (dental work, needles). None of the IAPS pictures used included social stimuli. Of the forty neutral images, twenty were selected to be used in critical trials and the remaining twenty were used in neutral trials. The dot-probe task was programmed using DMDX (Forster & Forster, 2003) and presented on a 15" Mac Book Pro operating Windows XP SP3.

2.3.2 Spence Children's Anxiety Scale (SCAS).

The Spence Children's Anxiety Scale (SCAS; Spence, 1998) was used to assess symptoms of anxiety. The SCAS consists of 45 items loading to six scales. The SCAS has good internal consistency, with α coefficients of greater than 0.90, adequate test-retest reliability over 6 months and good convergent and discriminant validity (Spence, 1998). In the current WS sample, the internal consistency was $\alpha = 0.798$. The SCAS have been used previously with a sample of adolescents and adults with WS (Dodd et al., 2009).

The SCAS was modified for participants who were no longer in school such that items that referred to school were edited to refer to work and items that referred to kids were edited to refer to people. For example the item 'I am popular amongst other kids my own age' was edited to read 'I am popular amongst other people my own age'. This was to ensure that the item content was appropriate for all participants.

2.4 Procedure

Informed consent was obtained from the participants or their parents, as appropriate. The study was approved by the Macquarie University Human Ethics Committee. Participants were tested individually in a quiet room either in their home or at the University. Participants sat approximately 60cm from the computer screen. The SCAS was completed by participants following the dot-probe task.

The dot-probe procedure was based on that used in previous research with children aged seven years and above (Mogg, Philippot et al., 2004; Roy et al., 2008; Waters, Mogg, Bradley, & Pine, 2008). Each trial began with a black fixation cross in the centre of a white background for 500ms followed by presentation of the two images on the left and right side of the fixation cross for 500ms. The inner edge of each image was 1.6cm away from the fixation cross and the images measured 8cm x 6cm. The visual angle separating the centre points of the two images was approximately 9°. The two images were then followed immediately by a probe presented in the centre of the space occupied by one of the two previous images. The probe was a light grey dot and measured 0.4cm diameter. The probe was presented 4.4cm away from the fixation cross. Participants were told to press the shift key that corresponded to the side the probe was on as quickly as possible. The probe remained on the screen until a response had

been made or until 10 seconds had passed. The participants' response to the probe, or the timeout of the probe, was followed by a 100 tick (approximately 1672ms) inter-trial interval. The fixation cross remained on the screen throughout each block. The experiment ran continuously within blocks then, at the end of each block, participants were told that they could take a break. They were instructed to press the spacebar when they were ready for the next block. At the start of the experiment, participants completed six practice trials and were given an opportunity to ask questions before the experimental trials began.

2.5 Data Preparation

Similar to previous studies (Dodd & Porter, 2010; Koster et al., 2004; Mogg, Bradley, Miles, & Dixon, 2004), incorrect trials and trials with timing errors (defined as trials with RTs of <200ms or >3000ms) were removed and a mean and standard deviation were calculated for each participant. RTs that were more than 2 standard deviations above each participant's mean were then also removed. The mean percentage of trials for which data was removed was 5.5% (SD 2.7). There were no significant differences between the WS group and either comparison group in the amount of data removed (p >0.2). All further analyses are conducted with mean RT data(the results are consistent when median RT is used).

Results

3.1 Dot-Probe Task

Table 2 shows the mean reaction time (RT) and standard deviations for each group (WS, CA, AC) on neutral (two neutral images), threat-congruent (the probe is located in the position of the threat image) and threat-incongruent (the probe is located in the position of the neutral image) trials[2].

3.1.1 Attention bias: congruent and incongruent trials.

A repeated-measures ANOVA was conducted with congruency (congruent/incongruent) as the within-subject variables and group (WS, CA, AC) as the between-subjects variable. The results indicated no significant main effect of congruency, F (1, 45) = 1.382, MSE = 482.765, p =0.246, but a significant main effect of group, F (2, 45) = 18.445, MSE = 350743.611, p <0.001, and a significant group by congruency interaction, F (2, 45) = 3.529, MSE = 1233.308, p =0.038. To explore this interaction, t-tests were conducted to examine the effect of congruency for each group independently. A Bonferroni corrected p-value of 0.017 (0.05/3) was used to indicate statistical significance. The WS group was significantly faster on congruent than incongruent trials, t (15) = -3.330, p=0.005 (d=0.20). The CA group was significantly faster on incongruent than congruent trials, t (15) = 3.032, p=0.008 (d=0.04). No significant effect of congruency was found for the AC group, t (15) = 0.143, p=0.888 (d=0.001).

To examine whether the size and direction of the bias differed significantly between groups (between-subjects bias), a bias score was calculated for each participant by subtracting their mean RT on congruent trials from their mean RT on incongruent trials. A positive number therefore indicated a bias towards threat and a negative number a bias away from threat. Mean bias scores are shown on Figure 1.

T-tests were conducted to compare the groups on overall bias, a p-value of 0.017 (0.05/3) was used to indicate statistical significance. A significant difference was found between the attention bias of the WS and CA groups, t (30) = 3.920, p<0.001 (d=1.39), but not between the WS and AC group, t (30) = 1.773, p=0.086 (d=0.63), or between the CA and AC groups, t (30) = -0.247, p=0.806 (d=0.09).

3.1.2 Vigilance and disengage effects.

Following Koster, et al. (2004) further t-tests were conducted to examine whether the biases observed were due to attentional vigilance or disengage effects by comparing the neutral condition with the congruent and incongruent conditions for each group. A corrected *p*-value of 0.008 (0.05/6) was used to indicate statistical significance. The WS group were significantly slower on incongruent trials than neutral trials, t (15) = -3.136, *p* =0.007 (*d*=0.16), but no difference was found between neutral and congruent trials, t (15) = 1.608, *p* = 0.598 (*d*=0.03). The CA group were slower on both congruent and incongruent trials than on neutral trials, this difference was significant for congruent trials, t (15) = -3.935, *p* = 0.001 (*d*=0.12), and approached significance for the incongruent l trials, t (15) = -2.976, *p* = 0.009 (*d*=0.007). No significant difference was found between the congruent and neutral, t (15) = 0.996, *p* = 0.335, or incongruent and neutral, t (15) = 1.408, *p* = 0.179, trials for the AC group.

3.2 The Relationship between Anxiety Symptoms and Attention Bias

The SCAS total scores (WS: M=29.75, sd=12.05, range = 10 - 58*;* CA: M=16.94, sd=10.47, range = 4 - 38*;* AC: M=26.13, sd=12.84, range = 1 - 35) suggest that there were some between-group differences in current anxiety symptoms, particularly between the WS and CA groups. As anticipated the WS group had the highest SCAS score. However the difference between the WS and AC group means is relatively small. It seems likely that this is due to the wide range of anxiety symptoms, including social anxiety symptoms, that the SCAS measures; WS participants would not be expected to score highly on the full range of anxiety symptoms. To examine whether the pattern of results on the dot-probe task was due to this difference in anxiety symptoms, the analyses were conducted again with total SCAS scores entered as a covariate.

The congruence by group interaction was no longer significant when SCAS total score was entered as a covariate, F (2, 45) = 2.617, MSE=926.358, *p*=0.084.

A between subjects t-test was conducted to compare attention bias between participants with WS who met criteria for an anxiety disorder (N=7) with those who did not (N=9). A significant difference was found between the groups, t(14)=-4.125, *p*=0.001, with those who met criteria for an anxiety disorder exhibiting a larger threat bias (M=37.07, sd=17.06) than those who did not (M=4.51, sd=14.52).

3.3 Bias, Age and Gender

To explore whether overall bias was related to chronological or mental age, Pearson product moment correlation coefficients were calculated. For the control sample, no significant correlations between bias scores and chronological age were found (p>0.1). For the WS group, no significant correlations between bias scores and either chronological or mental age were found. Further, independent samples t-tests were conducted to examine the effect of gender on bias. No significant effect of gender was found for the entire sample or any group in isolation (p>0.1).

Discussion

Neuroimaging research has reported atypical patterns of amygdala and PFC activation in WS, in response to both social and non-social stimuli, which are highly consistent with the WS behavioural phenotype (Haas et al., 2009; Meyer-Lindenberg et al, 2005, Munoz et al., 2010). Given the role these neural structures play in attentional vigilance and control (Bishop, 2007, 2009; Cisler & Koster, 2010; Pine, 2007), recent research has begun to explore attention biases

for emotional faces in WS (Dodd & Porter, 2010; Santos et al., 2010). The present study is the first study to examine attention bias for non-social threatening stimuli in this population. On the basis of previous findings, it was hypothesised that the WS group would exhibit a significant within-subjects bias to threat and that a significant between-subjects bias would be found when the WS group were compared to the typically developing control groups.

The results clearly supported the first hypothesis; a significant within-subjects attention bias towards threatening stimuli was observed in the WS group. In contrast, the chronological age matched control group exhibited a significant, although very slight, attention bias away from threat and no bias in either direction was found for the attentional control matched group. Although no bias was expected in either typically developing group, the findings for the chronological age control group are consistent with some previous studies reporting a subtle attention bias away from threat in non-anxious adults (Bar-Haim et al., 2007). The between-group comparisons provided some support for the second hypothesis as a significant difference in attention bias was found between the WS and CA groups and the difference between the WS and AC groups approached significance. This later comparison was supported by a large effect size (d=0.63). Taken together these findings suggest that WS is associated with an attention bias for threatening non-social stimuli.

Several recent studies have reported that individuals with WS exhibit deficits in response inhibition (Menghini, Addona, Costanzo, & Vicari, 2010; Mobbs et al., 2007) and broader executive function abilities including switching (Rhodes, Riby, Park, Fraser, & Campbell, 2010). These deficits in executive function have been linked with atypical frontal lobe activation (Mobbs et al., 2007) along with possible abnormalities in the left temporal lobe (Campbell et al., 2009). By comparing the WS group to a group of younger typically developing children matched

on attentional control ability, the influence of basic attentional control processes such as response inhibition and switching on task performance were able to be controlled. The results suggest, therefore, that individuals with WS exhibit an attention bias for threat that is, at least to some extent, independent of any general deficits in attentional control. Although this represents one of the strengths of the present design, it should be taken into consideration that the participants were matched on a verbally-based measure of attentional control whereas the dot-probe task relies on visual attention. Matching on a visually-based measure of attentional control may have provided a more stringent control. This highlights a point for consideration in future research with WS samples, which must be mindful of deficits in executive function in WS and carefully consider the measure used for group matching.

The results of the present study, showing an attention bias to threatening non-social images, and previous studies, showing increased attention to positive but not negative social stimuli in WS (Dodd & Porter, 2010; Santos et al., 2010), are highly consistent with the atypical pattern of amygdala activation reported in WS (Haas et al., 2009; Meyer-Lindenberg et al., 2005; Munoz et al., 2010); stimuli that lead to elevated amygdala activation in WS are also the subject of attentional biases and stimuli that do not lead to elevated amygdala activation are not the subject of attentional biases (Dodd & Porter, 2010; Santos et al., 2010). Given the clear parallels between these findings from neuroimaging and cognitive research and the strong theoretical support for a link between amygdala activation and attention, these results provide preliminary evidence that atypical amygdala activation in WS may be associated with biases in attention.

To more closely consider the processes that might drive this link between amygdala activation and attention bias, it is important to consider the role of the PFC and related cortical structures. As discussed, the amygdala underpins the bottom-up threat detection mechanism

and affects initial orienting of attention (Bishop, 2007, 2009; Cisler & Koster, 2010; Pine, 2007). In relation to the dot-probe task, amygdala activation has been linked with faster responses on congruent trials, a measure of attentional vigilance (Carlson, Reinke & Habib, 2009). In contrast, the PFC is involved in the top-down control of attention and has been linked to difficulties disengaging attention from threat in the dot-probe task (Bishop, 2007, Cisler & Koster, 2010). It is interesting, therefore, that the attention bias found in the present research and in Dodd and Porter (2010) was driven by difficulties *disengaging* attention. To clarify, the WS participants were not faster to respond to a probe that followed a threat image, which would suggest attentional vigilance. Instead, the presence of the threatening image slowed the WS participants' responses when they were required to shift their attention away from the threatening scene to a probe on the other side of the screen. It seems plausible therefore that the attention bias observed in the present research and in previous research with WS is underpinned by the abnormalities in the PFC – amygdala pathway consistent with those reported by Meyer-Lindenberg et al. (2005) and, more recently, by Munoz et al. (2010).

This possible link between atypical patterns of neural activation and attention bias in WS lays the foundation for several exciting areas for future research. An important initial step in extending these findings will be to replicate them in other WS samples using different methodologies. One particularly useful way of examining attentional deployment is the use of eye-tracking, which could certainly provide rich data on patterns of attentional deployment across different stimuli (e.g. Riby & Hancock, 2009a). In order to make explicit links between neural activation and attention bias in WS, it will be essential to combine neuroimaging with behavioural measures of cognitive bias as has been used in recent research with typically developing adults (Carlson et al., 2009). A further interesting area of research will be to examine

how heterogeneity in WS deletions is associated with individual differences in neural activation and attentional bias.

Although the findings of the present research indicate that WS is associated with an attention bias for threatening non-social stimuli, it is important to note that this attention bias was closely related to current anxiety symptoms and diagnoses in WS. When anxiety symptoms were controlled for statistically no between-group differences in attention bias were found. Furthermore, WS participants who met criteria for an anxiety disorder exhibited significantly larger attention biases than those who did not. This raises a number of interesting points for consideration. Firstly, it is not possible to determine whether the attention bias observed in the present research is simply a consequence of the elevated anxiety in this population or whether the attention bias plays a role in the onset or maintenance of anxiety in WS. Longitudinal research or research using bias modification procedures, in which cognitive bias is increased or decreased using training paradigms (MacLeod, Rutherford, Campbell, Ebsworthy & Holker, 2002; See, MacLeod, & Bridle, 2009), is required to address this question. On a related point, it is also unclear to what extent the atypical amygdala activation reported by Meyer-Lindenberg et al. (2005) and Munoz et al. (2010) is related to current anxiety symptoms in their WS participants as anxiety was not thoroughly assessed using diagnostic measures or symptom scales in these studies. It remains possible that the elevated amygdala activation in response to threatening non-social scenes and the attention bias found in the present research are consequences of elevated anxiety in this population and do not play a causal role. This should, however, not detract from the significance of the present findings which: (1)demonstrate that the dissociation between social and non-social anxiety in WS can be observed at the cognitive level; (2) highlight the potential role of attention processing in linking atypical neural activation

in WS with the WS behavioural phenotype; (3) provide the first evidence that anxiety in WS is associated with biased attentional processing similar to that observed in the typically developing population (Bar-Haim et al., 2007).

In demonstrating that anxiety in WS is associated with cognitive biases similar to those seen in the typically developing population, this study provides theoretical support for the use of cognitive therapies, initially designed for use with typically developing adults and children, with the WS population. Given the elevated rates of GAD and Specific Phobia seen in this population, and the paucity of research considering treatment options, it is essential that future research examine the efficacy of various cognitive behavioural techniques with individuals with WS. Recent case studies provide initial indication that these techniques may be useful for the treatment of anxiety in WS (Klein-Tasman & Albano, 2007; Phillips & Klein-Tasman, 2009).

The findings need to be considered within the context of the study's strengths and limitations. Firstly, due to the cognitive demands of the task, we decided to only invite individuals with WS who had a mild to moderate intellectual impairment and a mental age of at least 6.5 years to participate. As WS is a rare genetic disorder, this resulted in a small sample size. Participants were recruited nationally to ensure the sample size was as large as possible and the resulting participant numbers are comparable to many recent studies conducted with this population (Krajcsi, Lukacs, Igacs, Racsmany, & Pleh, 2009; Riby & Hancock, 2009b; Vicari, Bellucci, & Carlesimo, 2006). These results should, however, be considered preliminary and it will be useful for future research to replicate these findings in other samples of individuals with WS. Secondly, the basic dot-probe task was used over the probe-discrimination task in order to keep the cognitive load of the task as low as possible for the WS participants and younger mental-age matched controls. Although this task is used frequently in published research, it has

been argued that the probe-discrimination task may provide a better measure of attention allocation (see Mogg & Bradley, 1999 for a review of the relative merits of the two tasks).

In addition to the use of an attentional control group discussed previously, further strengths of the study lie in the use of a methodology that allows straightforward comparison with research into social processing in WS, and the assessment of clinical anxiety diagnoses in the WS group and anxiety symptoms in all groups. As there are no measures of anxiety symptoms currently validated for use with both WS participants and the typically developing populations, a symptom-based measure that has been used with WS samples previously was chosen. The measure showed good internal consistency with the present WS sample and it would be useful to further validate this measure for use in future research with this population.

In summary, the present research provides the first evidence of an attention bias for non-social threat in WS. This finding lays the foundation for several avenues of future research including: exploring the relationship between atypical amygdala activation, attention bias and the WS behavioural phenotype, examining the role of attention biases in the onset and maintenance of anxiety in WS and further examining the efficacy of cognitive therapies to treat anxiety in WS.

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References

American Psychiatric Association, A. P. (1994). *Diagnostic and statistical manual of mental disorders (4th ed.)*. Washington, DC: American Psychiatric Association.

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: A meta-analytic study. *Psychological Bulletin, 133(1),* 1-24. doi:10.1037/0033-2909.133.1.1

Bellugi, U., Lichtenberger, L., Jones, W., Lai, Z., & St (2000). I. The neurocognitive profile of williams syndrome: A complex pattern of strengths and weaknesses. Journal of Cognitive *Neuroscience, 12(1),* 7-29. doi:10.1162/089892900561959

Bishop, S.J. (2007). Neurocognitive mechanisms of anxiety: an integrative account , *Trends in Cognitive Sciences, 11 (7)*, 307-316. doi:10.1016/j.tics.2007.05.008

Bishop S.J. (2009). Trait anxiety and impoverished prefrontal control of attention. *Nature Neuroscience, 12,* 92–98. doi: 10.1038/nn.2242

Brown, V., Johnson, M. H., Paterson, S. J., Gilmore, R., Longhi, E., & Karmiloff-Smith, A. (2003). Spatial representation and attention in toddlers with williams syndrome and down syndrome. . *Neuropsychologia, 41,* 1037-1046. doi:10.1016/S0028-3932(02)00299-3

Campbell, L.E., Daly, E., Toal, F., Stevens, A., Azuma, R., Karmiloff-Smith, A…Murphy, M.K.C. Brain structural differences associated with the behavioural phenotype in children with Williams syndrome. *Brain Research, 1258,* 96-107. doi: 10.1016/j.brainres.2008.11.101

Carlson, J.M., Reinke, K.S., & Habib, R. (2009). A left amygdala mediated network for rapid orienting to masked fearful faces. *Neuropsychologia, 47 (5),* 1386 – 1389. doi: doi:10.1016/j.neuropsychologia.2009.01.026

Cisler, J.M., & Koster, E.H.W. (2010). Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. Clinical psychology review 30(2),203-16. doi:10.1016/j.cpr.2009.11.003

Cornish, K., Scerif, G., & Karmiloff-Smith, A. (2007). Tracing syndrome-specific trajectories of attention across the lifespan. *Cortex, 43(6),* 672-685. doi:10.1016/S0010-9452(08)70497-0

Derryberry, D., & Reed, M. A. (2002). Anxiety-related attentional biases and their regulation by attentional control. *Journal of Abnormal Psychology, 111*, 225-236. doi:10.1037/0021-843X.111.2.225

Dodd, H. F., & Porter, M. A. (2009). Psychopathology in Williams syndrome: The effect of individual differences across the life span. *Journal of Mental Health Research in Intellectual Disabilities, 2 (2)*, 89-109. doi:10.1080/19315860902725867

Dodd, H. F., Schniering, C. A., & Porter, M. A. (2009). Beyond behaviour: Is social anxiety low in williams syndrome? *Journal of Autism and Developmental Disorders, 39 (12),* 1673-1681. doi:10.1007/s10803-009-0806-4

Dodd, H.F., & Porter, M.A. (2010). I see happy people: attention towards happy but not angry facial expressions in Williams syndrome. *Cognitive Neuropsychiatry*. Advance online publication. doi:10.1080/13546801003737157

Dodd, H.F. & Porter, M.A. (In Press). Interpretation of ambiguous situations: evidence for a dissociation between social and physical threat in Williams syndrome. *Journal of Autism and Developmental Disorders*.

Doyle, T. F., Bellugi, U., Korenberg, J., & Graham, J. (2004). "Everybody in the world is my friend" Hypersociability in young children with Williams syndrome. *American Journal of Medical Genetics, 124A (3)*, 263-273. doi:10.1002/ajmg.a.20416

Dykens, E. M. (2003). Anxiety, fears, and phobias in persons with williams syndrome. *Developmental Neuropsychology, 23(1-2),* 291-316. doi:10.1207/S15326942DN231&2_13

Einfeld, S. L., Tonge, B. J., & Florio, T. (1997). Behavioral and emotional disturbance in individuals with williams syndrome. *American Journal on Mental Retardation, 102(1)*, 45-53. doi:10.1352/0895-8017(1997)102<0045:BAEDII>2.0.CO;2

Espy, K.A. (1997). The shape school: Assessing executive function in preschool children. *Developmental Neuropsychology, 13 (4),* 495-499. Doi: 10.1080/87565649709540690

Ewart, A., Morris, C. A., Atkinson, D., Jin, W., Sternes, K., Spallonem, P.,…Keating, M.T. (1993). Hemizygosity at the elastin locus in a developmental disorder, williams syndrome. *Nature Genetics, 5*, 11-16. doi:10.1038/ng0993-11

Forster, K. I., & Forster, J. C. (2003). DMDX: A windows display program with millisecond accuracy. *Behavior Research Methods, Instruments & Computers, 35(1)*, 116-124. Retrieved from http://brm.psychonomic-journals.org/

Fryssira, H., Palmer, R., Hallidie-Smith, K. A., Taylor, J., Donnai, D., & Reardon, W. (1997). Fluorescent in situ hybridisation (FISH) for hemizygous deletion at the elastin locus in patients with isolated supravalvar aortic stenosis. *Journal of Medical Genetics, 34(4)*, 306-308. doi:10.1136/jmg.34.4.306

Haas, B. W., Mills, D., Yam, A., Hoeft, F., Bellugi, U., & Reiss, A. (2009). Genetic influences on sociability: Heightened amygdala reactivity and event-related responses to positive

social stimuli in Williams syndrome. *Journal of Neuroscience, 29 (4)*, 1132-1139. doi:10.1523/JNEUROSCI.5324-08.2009

Jarvinen-Pasley, A., Bellugi, U., Reilly, J., Mills, D.L., Galaburdam A., Reiss, A.L., & Korenberg, J.R. (2008). Defining the social phenotype in Williams syndrome: a model for linking gene, the brain, and behaviour. *Development and Psychopathology, 21 (1),* 1-35. doi: 10.1017/S0954579408000011.

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., …Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (k-sads-pl): Initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry, 36*, 980-988. doi:10.1097/00004583-199707000-00021

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry, 62 (6)*, 617-627. doi:10.1001/archpsyc.62.6.617

Kindt, M., Bierman, D., & Brosschot, J.F. (1997). Cognitive bias in spider fear and control children: assessment of emotional interference by a card format and a single-trial format of the stroop task. *Journal of Experimental Child Psychology, 66 (20),* 163-179. doi:10.1006/jecp.1997.2376

Koster, E. H., Crombez, G., Verschuere, B., & De Houwer, J. (2004). Selective attention to threat in the dot probe paradigm: Differentiating vigilance and difficulty to disengage. *Behaviour Research and Therapy, 42,* 1183-1192. doi:10.1016/j.brat.2003.08.001

Krajcsi, A., Lukacs, A., Igacs, J., Racsmany, M., & Pleh, C. (2009). Numerical abilities in williams syndrome: Dissociating the analogue magnitude system and verbal retrieval. *Journal of*

Clinical and Experimental Neuropsychology, 31(4), 439-446. doi:10.1080/13803390802244126

Lang, P. J., Bradkey, M. M., & Cuthbert, B. N. (2005). International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical report A-6. Gainesville, FL: University of Florida.

Lewinsohn, P. M., Clarke, G. N., Seeley, J. R., & Rohde, P. (1994). Major depression in community adolescents: Age at onset, episode duration and time to recurrence. *Journal of the American Academy of Child and Adolescent Psychiatry, 33 (6)*, 809-818. doi:10.1097/00004583-199407000-00006

Leyfer, O. T., Woodruff-Borden, J., Klein-Tasman, B. P., Fricke, J. S., & Mervis, C. B. (2006). Prevalence of psychiatric disorders in 4 to 16-year-olds with williams syndrome. *American Journal of Medical Genetics, Part B: (Neuropsychiatric Genetics), 141B,* 615-622. doi:10.1002/ajmg.b.30344

Martens, M.A., Wilson, S.J., Dudgeon, P., & Reutens, D.C. (2009). Approachability and the amygdala: Insights from Williams syndrome. *Neuropsychologia, 47 (12),* 2446-2453. doi:10.1016/j.neuropsychologia.2009.04.017

Mathews*, A., &* Mackintosh*, B. (*1998*).* A cognitive model of selective processing in anxiety. *Cognitive Therapy and Research, 22 (6),* 539-560. doi: 10.1023/A:1018738019346

MacLeod, C., Rutherford, E., Campbell, L., Ebsworthy, G., & Holker, L. (2002). Selective attention and emotional vulneravility: Assessing the causal bias of their association through the experimental maniulation of attentional bias. *Journal of Abnormal Psychology, 111*, 107-123. doi:10.1037/0021-843X.111.1.107

Menghini, D., Addona, F., Costanzo, F., & Vicari, S. (2010). Executive functions in individuals with Williams syndrome, *Journal of Intellectual Disability Research, 54 (5),* 418-432. doi: 10.1111/j.1365-2788.2010.01287.x

Mervis, C. B., & Klein-Tasman, B. P. (2000). Williams syndrome: Cognition, personality, and adaptive behavior. *Mental Retardation and Developmental Disabilities Research Reviews, 6(2)*, 148-158. doi:10.1002/1098-2779(2000)6:2<148::AID-MRDD10>3.0.CO;2-T

Meyer-Lindenberg, A., Hariri, A. R., Munoz, K. E., Mervis, C. B., Mattay, V. S., Morris, C. A., & Berman, K.F. (2005). Neural correlates of genetically abnormal social cognition in Williams syndrome. *Nature Neuroscience, 8*, 991-993. doi:10.1038/nn1494

Mobbs, D., Eckert, M.A., Mills, D., Korenberg, J., Bellugi, U., Galaburda, A.M., & Reissm A.L. (2007). Frontostriatal dysfunction during response inhibition in Williams syndrome. *Biological Psychiatry, 62 (3),* 256-261. doi: 10.1016/j.biopsych.2006.05.041

Mogg, K., & Bradley,B.P. (1999). Some methodological issues in assessing attentional biases for threatening faces in anxiety: a replication study using a modified version of the probe detection task, *Behaviour Research and Therapy, 37,* 595–604. doi:10.1016/S0005-7967(98)00158-2

Mogg, K., Bradley, B. P., Miles, F., & Dixon, R. (2004). Time course of attentional bias for threat scenes: Testing the vigilance-avoidance hypothesis. *Cognition & Emotion, 18(5)*, 689-700.
doi:10.1080/02699930341000158

Mogg, K., Philippot, P., & Bradley, B. P. (2004). Selective attention to angry faces in clinical social phobia. *Journal of Abnormal Psychology, 113(1)*, 160-165. doi:10.1037/0021-843X.113.1.160

Munoz, K.E., Meyer-Lindenberg, A., Hariri, A.R., Mervis, C.B., Mattay, V.S., Morris, C.A., & Berman, K.F. Abnormailities in neural processing of emotional stimuli in Williams syndrome vary according to social vs. non-social. *Neuroimage, 50 (1),* 340-346. doi:10.1016/j.neuroimage.2009.11.069

Pine, D. (2007). Research review: A neuroscience framework for pediatric anxiety disorders. *Journal of Child Psychology and Psychiatry, 48 (7),* 631-648. Doi:10.1111/j.1469-7610.2007.01751.x

Riby, D. M., & Hancock, P. J. B. (2009b). Do faces capture the attention of individuals with williams syndrome or autism? Evidence from tracking eye movements. *Journal of Autism & Developmental Disorders, 39 (3)*, 421-431. doi:10.1007/s10803-008-0641-z

Riby, D., & Hancock, P. (2009b). Looking at movies and cartoons: Eye-tracking evidence from williams syndrome and autism. *Journal of Intellectual Disability Research, 53(2),* 169-181. doi:10.1111/j.1365-2788.2008.01142.x

Rhodes, S.M., Riby, D.M., Park, J., Fraser, E., & Campbell, L.E. (2010). Executive neuropsychological functioning in individuals with Williams syndrome. *Neuropsychologia, 48 (5),* 1216-1226. doi: 10.1016/j.neuropsychologia.2009.12.021

Roy, A. K., Vasa, R. A., Bruck, M., Mogg, K., Bradley, B. P., Sweeney, M.,…The CAMS Team. (2008). Attention bias toward threat in pediatric anxiety disorders. *Journal of the American Academy of Child & Adolescent Psychiatry, 47(10)*, 1189-1196. doi:10.1097/CHI.0b013e3181825ace

Salemink, E., van den Hout, M. A., & Kindt, M. (2007). Selective attention and threat: Quick orienting versus slow disengagement and two versions of the dot probe task. *Behaviour Research and Therapy, 45*, 607-615. doi:10.1016/j.brat.2006.04.004

Santos, A., Silva, C., Rosset, D., & Deruelle, C. (2010). Just another face in the crowd: Evidence for decreased detection of angry faces in children with Williams syndrome. *Neuropsychologia*, *48 (4),*1071-8. doi:10.1016/j.neuropsychologia.2009.12.006

See, J., MacLeod, C., & Bridle, R. (2009). The reduction of anxiety vulnerability through the modification of attentional bias: A real-world study using a home-based cognitive bias modification procedure. Journal of Abnormal Psychology, 118(1), 65-75. doi:10.1037/a0014377

Spence, S. H. (1998). A measure of anxiety symptoms among children. Behaviour Research and Therapy, 36, 545-566. doi:10.1016/S0005-7967(98)00034-5

Udwin, O. (1990). A survey of adults with williams syndrome and idiopathic infantile hypercalcaemia. *Developmental Medicine & Child Neurology, 32(2)*, 129-141. http://www.wiley.com/bw/journal.asp?ref=0012-1622

Vicari, S., Bellucci, S., & Carlesimo, G. A. (2006). Evidence from two genetic syndromes for the independence of spatial and visual working memory. *Developmental Medicine and Child Neurology, 48*, 126-131. doi:10.1017/S0012162206000272

Waters, A. M., Lipp, O. V., & Spence, S. H. (2004). Attentional bias toward fear-related stimuli: An investigation with nonselected children and adults and children with anxiety disorders. *Journal of Experimental Child Psychology 89*, 320-337. doi:10.1016/j.jecp.2004.06.003

Waters, A. M., Mogg, K., Bradley, B. P., & Pine, D. S. (2008). Attentional bias for emotional faces in children with generalized anxiety disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 47(4),* 435-442. doi:10.1097/CHI.0b013e3181642992

Woodcock, R. W., & Johnson, M. B. (Eds.). (1989, 1990). *Woodcock-Johnson psycho-educational battery-Revised*. Itascam IL: Riverside.

Yiend, J., & Mathews, A. (2001). Anxiety and attention to threatening pictures. *The Quarterly Journal of Experimental Psychology, 54A*, 665-681. doi:10.1080/02724980042000462

Table 1

Mean and standard deviation of age (years), Shape School efficiency score and gender data for all groups

	N	Gender (M;F)	Chronological Age M (sd)	Mental Age M (sd)	Shape School Efficiency Score M (sd)
Williams syndrome group	16	9;7	21.04 (6.20)	8.09 (1.04)	0.37 (0.11)
Chronological age matched group	16	9;7	21.05 (5.97)	-	-
Attentional Control matched group	16	9;7	8.14 (1.23)	-	0.41 (0.10)

Table 2

Mean and standard deviation of RTs (ms) for each group and condition

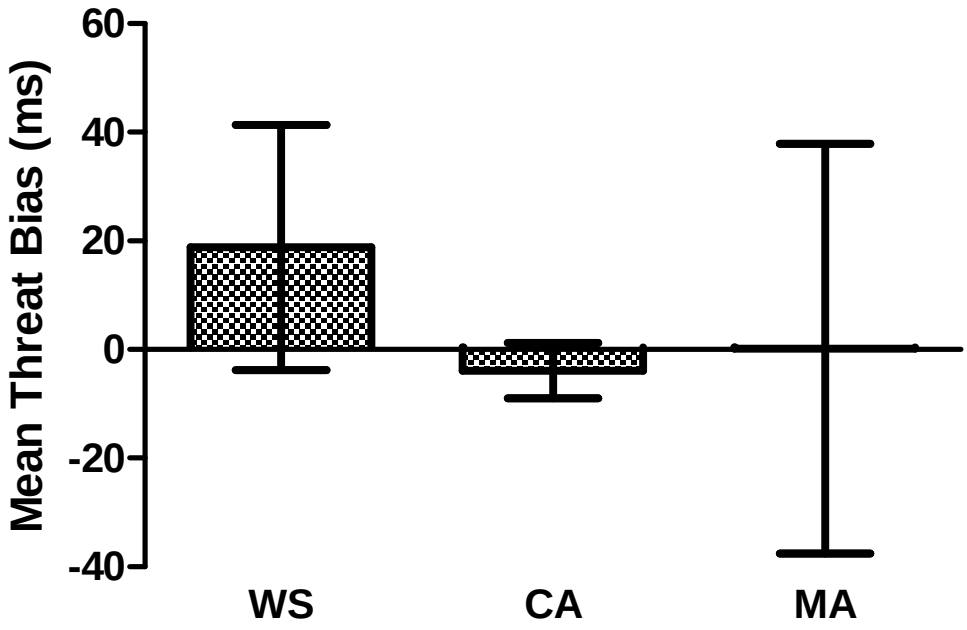
Condition	Williams syndrome M (sd)	Chronological Age M (sd)	Attentional Control M (sd)
Neutral-Neutral	627 (95)	421 (87)	561 (87)
Threat-congruent	624 (97)[a]	432 (93)[ab]	575 (116)
Threat-incongruent	643 (94)[b]	428 (91)[b]	574 (98)

[a]Significant difference between threat-congruent and threat-incongruent conditions (p<0.05).

[b]Condition significantly different to Neutral-neutral condition (p<0.05).

Figure captions

Figure 1: Mean attention bias for each group (error bars show 1 standard deviation). Positive scores indicate bias towards threat, negative scores indicate bias away from threat (WS = Williams syndrome; CA = Chronological Age; AC = Attentional Control).



Footnotes

[1] IAPS images used. Threat pictures: 1050, 1052, 1201, 1220, 1300, 1525, 1930, 1931, 1932, 5971, 6610, 6940, 8485, 9584, 9592, 9600, 9620, 9621, 9622, 9630. Neutral Pictures (Threat-Neutral trials): 1900, 5500, 5531, 5720, 5900, 7002, 7036, 7050, 7057, 7100, 7217, 7234, 7491, 7504, 7546, 7547, 7560, 7595, 7700, 7710. Neutral pictures (Neutral-Neutral trials): 5395, 5535, 5740, 7041, 7052, 7056, 7058, 7090, 7175, 7224,5130, 5731, 6150, 7000, 7006, 7009, 7037, 7211, 7233, 7705. Independent sample t-tests were conducted to compare image types on valence, arousal and dominance. Significant differences were found between the threat and neutral images on each dimension ($p<0.001$). The mean and standard deviation for both colour and luminosity were measured for each image using Photoshop. No significant differences were found between the threat and neutral images on any of these measures ($p>0.05$)

[2] The mean values shown in Table 2 suggest that the groups differed in their reaction time to neutral trials. As we were specifically interested in the congruency by group interaction, rather than overall group effects, this difference in neutral RT should not affect the statistical analyses that follow.