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Individual differences in social behavior predict amygdala response to fearful facial expressions in Williams syndrome☆

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ABSTRACT

Williams syndrome (WS) is a genetic condition often paired with abnormal social functioning and behavior. In particular, those with WS are characterized as being relatively hypersocial, overly emotional/empathic, and socially uninhibited or fearless. In addition, WS is associated with abnormal amygdala structure and function. Very little is known however about the relationship between specific social behaviors and altered amygdala function in WS. This study was designed to compare three models that relate abnormal social behavior with amygdala function in WS (indiscriminate sociability, emotional and empathic sociability and social fearlessness). We used a social behavior assessment procedure (Salk Institute Sociability Questionnaire), functional magnetic resonance imaging and an implicit emotion face processing task to test these models. Our findings provide support for a model of abnormal social fearlessness by showing that in WS, abnormal amygdala response to fear is paired with an increased tendency to approach strangers. Specifically, individuals with WS that exhibited less amygdala response to fearful facial expressions (compared to neutral) also exhibited an increased tendency to approach strangers. These findings contribute to our understanding of social and emotional functioning in neurodevelopmental conditions and provide evidence that in WS, amygdala response to fear modulates social behavior.

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1. Introduction

Williams syndrome (WS) is a neurodevelopmental condition caused by a hemizygous microdeletion on chromosome 7q11.23. WS is often paired with a distinctive, abnormal social and emotional phenotype. In particular, those with WS are often described as being relatively hypersocial (Bellugi, Adolphs, Cassady, & Chiles, 1999), overly emotional/empathic (Klein-Tasman & Mervis, 2003) and socially uninhibited or fearless (Gosch & Pankau, 1994; Meyer-Lindenberg, Mervis, & Berman, 2006). In terms of the brain, evidence suggests that alterations of the amygdala may in part contribute to the observed abnormal social and emotional phenotype in WS (Haas et al., 2009; Martens, Wilson, Dudgeon, & Reutens, 2009; Meyer-Lindenberg et al., 2005). Recently, brain-imaging studies have begun to explore the neural correlates of individual differences of social behavior in WS. For example, Martens and colleagues (2009) demonstrated that in WS, individual differences in social behaviors, such as with approachability biases, are associated with alterations in amygdala volume. Although studies have indicated that functional abnormalities of the amygdala occur in WS (relative to healthy controls) and that individual differences in social behaviors are associated with amygdala *structure* in WS (Martens et al., 2009), very little is known regarding the relationship between individual differences in social behavior and amygdala *function* in WS. This study was designed to investigate the relationship between social behavior and amygdala function in WS. We used functional Magnetic Resonance Imaging (fMRI) and an implicit emotion face processing task to test three models that relate abnormalities of social behavior with amygdala function in WS (Fig. 1).

One model posits that individuals with WS tend to display abnormal *indiscriminate sociability* (Doyle, Bellugi, Korenberg, & Graham, 2004; Einfeld, Tonge, & Florio, 1997). This model describes those with WS as being abnormally social and driven towards social interaction independent of emotional valence or arousal and is supported by studies showing that relative to mental and age-matched controls, individuals with WS tend to be rated as generally more "overly-friendly" (Mervis & Klein-Tasman, 2000), people-oriented and gregarious (Klein-Tasman & Mervis, 2003). In addition, as compared to controls, those with WS rate facial expressions as more

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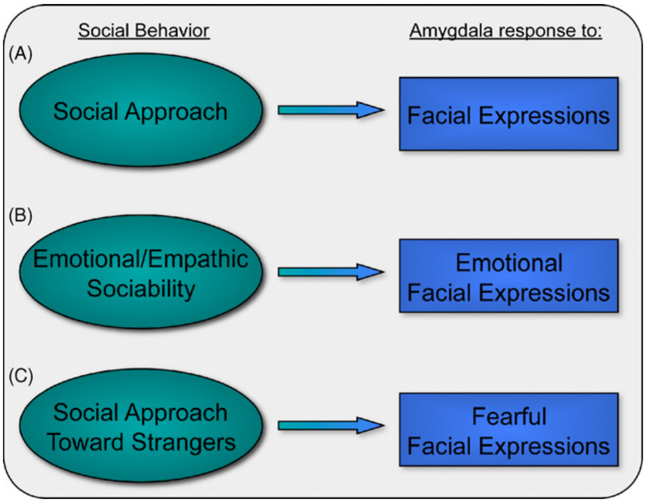

Fig. 1. Model based hypotheses relating social behavior with amygdala function in WS. We predicted that if abnormal *indiscriminate sociability* is associated with amygdala function in WS (A), we would observe a relationship between social approach scores and amygdala response to facial expressions (fearful, happy and neutral combined) compared to scrambled images. We predicted that if abnormal *emotional and empathic sociability* is associated with amygdala function in WS (B), we would observe a relationship between emotional/empathic sociability scores and amygdala response to emotional facial expressions (fear and happy, combined) compared to neutral. We predicted that if abnormal *social fearlessness* is associated with amygdala function in WS (C), we would observe a relationship between social approach towards strangers and amygdala response to fearful facial expressions compared to neutral.

approachable (Bellugi et al., 1999) and tend to exhibit greater gaze duration towards socially relevant scenes (Riby & Hancock, 2008) and faces (Riby & Hancock, 2009). Some studies however, have also found normal approachability towards both negative and positive expressions in WS (Porter, Coltheart, & Langdon, 2007). Taken together, several studies provide evidence that WS is associated with abnormalities in overt social behavior and attention towards socially relevant information such as facial expressions. We predicted that if functional abnormalities of the amygdala are associated with *indiscriminate sociability* in WS, then we would observe a positive relationship between individual differences in social approach related behaviors and amygdala response to all facial expressions (fearful, happy and neutral combined compared to scrambled images) (Fig. 1A and Fig. 2).

A second model posits that individuals with WS tend to display abnormal *emotional and empathic sociability*. This model describes those with WS as being highly emotionally responsive and particularly tuned to the affective states of others and is supported by studies showing that relative to controls, those with WS are rated higher in empathy (Klein-Tasman & Mervis, 2003), temperamental intensity (Tomc, Williamson, & Pauli, 1990) and tend to be relatively over-affectionate (Davies, Udwin, & Howlin, 1998). In addition, as compared to controls, those with WS are more emotionally responsive during social interaction (Fidler, Hepburn, Most, Philofsky, & Rogers, 2007), rate happy facial expressions as more approachable (Frigerio et al., 2006) and utilize more emotionally expressive language (Jones et al., 2000; Losh, Bellugi, Reilly, & Anderson, 2000). Other studies however, have demonstrated reduced expressive language in WS (Laws & Bishop, 2004). Together, several studies provide evidence that WS is associated with abnormalities in emotional and empathic processing. We predicted that if functional abnormalities of the amygdala are associated with the tendency to display *emotional and empathic sociability* in WS, we would observe a positive relationship between individual differences in emotional and empathic approach related behaviors and amygdala response to emotional (both fearful and happy) facial expressions (compared to neutral faces) (Fig. 1B and Fig. 2).

Lastly, a third model posits that individuals with WS are socially uninhibited with strangers and that they display abnormal *social fearlessness*. This model describes those with WS as being relatively unresponsive to social fear paired with an inappropriate tendency to approach strangers and is supported by studies showing that relative to controls, those with WS exhibit an inability to detect and respect social danger signals (Meyer-Lindenberg et al., 2006) and are less reserved towards strangers (Gosch & Pankau, 1994). In addition, as compared to controls, those with WS exhibit lower amygdala response to fearful facial expressions (Haas et al., 2009; Meyer-Lindenberg et al., 2005) and are less able to perceive negatively valenced emotional facial and vocal expressions (Plesa-Skwerer, Faja, Schofield, Verbalis, & Tager-Flusberg, 2006). Taken together, these studies provide evidence that WS is associated with an abnormal social fear response and an increased tendency to approach strangers. We predicted that if functional abnormalities of the amygdala are associated with the tendency to display *social fearlessness* in WS, we would observe a relationship between individual differences in social approach related behaviors towards strangers and amygdala response to fearful facial expressions (compared to neutral) (Fig. 1C and Fig. 2).

2. Methods

2.1. Participants

Twelve adult participants with WS (8 females; mean (*M*) age = 29.46, standard deviation (SD) = 8.07, range = 18.03–43.58, 8 right handed) were recruited for this study. Subjects were excluded if they reported any current use of mood-altering medication, substance abuse during the 6 months prior to scan or any standard MRI contraindications. Each participant was recruited as part of an ongoing multicenter

Fig. 2. Examples of stimuli used in the experimental paradigm. Participants were presented with photographs of faces conveying fearful, happy, neutral expressions and scrambled images. Participants were instructed to judge if each stimulus was either male, female or scrambled as quickly and as accurately as possible. Behavioral responses were collected within the 2000 ms following the onset of each stimulus.

collaborative research study focused on investigating the functional neuroanatomy of WS. The diagnosis of WS was genetically confirmed in all participants using the fluorescent *in situ* hybridization test for a deletion of one copy of the elastin gene on chromosome 7. The participants in this study are a subset of those of which that have previously been reported on in other studies from our laboratory (Haas et al., 2009; Hoeft et al., 2007).

2.2. Assessment of social behavior

Social behavior was assessed with the Salk Institute Sociability Questionnaire (SISQ) (Doyle et al., 2004; Jones et al., 2000). The SISQ is a parent-report questionnaire that yields three composite scores: global sociability; social approach (comprised of the two subscales approach strangers and approach familiars); and emotional and empathic sociability. While the SISQ has yet to be normed, it has been used to explore social behavior in young adults, children, special populations (Williams syndrome, autism, Down syndrome), across cultures (Doyle et al., 2004; Jones et al., 2000; Zitzer-Comfort, Doyle, Masataka, Korenberg, & Bellugi, 2007), and has been demonstrated to have face validity. (See Jarvinen-Pasley et al., 2008 for a review.)

Parents rate their child's (including their adult child's) current social tendencies on a seven-point Likert scale with low-, mid-, and high-endpoint labels tailored to each individual item. The social approach scale consists of items that assess the individual's tendency to approach others in general. Representative items on the social approach scale consist of statements such as "My child will spontaneously greet or approach: a member of his/her immediate family?" or "a familiar peer", rated on a scale of 1 (very rarely) to 7 (very often). Items assessing emotional and empathic social behavior ask parents to rate their child's tendency to empathize with others, the accuracy of their emotional evaluations of others, their eagerness to please other people, and their abilities to remember names and faces (the mean of 4 items yields a "emotional and empathic sociability" score). Lastly, the approach strangers scale consists of statements such as "My child will spontaneously greet or approach: an unfamiliar adult", or "How would you compare your child's tendency to approach strangers with an average child of the same age?" where parents respond on a scale ranging from 1 ('approaches much less') to 7 ('approaches much more').

2.3. Task design

The stimuli consisted of color pictures of headshots of young adults displaying fearful, happy, neutral expressions and scrambled images (Fig. 2). One hundred undergraduate students were trained to display emotional expressions depicting a variety of emotional expressions that included fearful, happy and neutral. Each photograph was rated by 20 students on a 5-point Likert scale for how typical each photograph depicted each emotional category with 1 scored as "not at all like the emotion" and 5 scored as "very characteristic of the emotion." Only stimuli that had the highest average ratings for a given target emotion were selected for that category. Fearful face stimuli were rated as more fearful than neutral ($t = 16.01$, $p < .001$), and happy faces ($t = 18.65$, $p < .001$); happy face stimuli were rated as more happy than fearful ($t = 61.93$, $p < .001$) and neutral faces ($t = 49.66$, $p < .001$); neutral face stimuli were rated as more neutral than fearful ($t = 36.63$, $p < .001$) and happy faces ($t = 47.54$, $p = .001$). A group of randomly selected photographs of male and female neutral facial expressions was selected in order to create scrambled isoluminant images. Each scrambled image was created by randomly dividing each photograph into 256 parts as in a previous study (Mobbs et al., 2004).

Stimuli were presented using an event-related design with four experimental conditions (fearful, happy, neutral and scrambled) and a resting baseline. Subjects were instructed to judge if each face was either male, female or scrambled by responding with their right index, middle or ring finger, respectively, as quickly and as accurately as possible. There were a total of 30 trials per condition and each stimulus was presented for 1750 ms, followed by a 250 ms duration fixation cross. There were 2 runs, with each run lasting 4 min 32 s. Behavioral responses were collected within the 2000 ms following the onset of each stimulus. Only the first response was recorded following the presentation of each stimulus.

2.4. fMRI data acquisition

Whole-brain-imaging data were acquired on a GE-Signa 3 T scanner (General Electric, Milwaukee, WI). For structural whole brain images, a three-dimensional high-resolution spoiled gradient scan (SPGR) (repetition time, 24 ms; echo time, 5 ms; flip angle, 15°; number of excitations, 2; matrix size, 256 × 256; field of view, 24 cm; slice thickness, 1.2 mm; 124 contiguous slices) and a T1 in-plane scan (14 slices, 5 mm thickness; oriented parallel to the line between the anterior and posterior commissure) were conducted. Functional images were acquired using a spiral in/out T2*-weighted imaging sequence and were obtained using a flip angle of 80°, repetition time (TR) = 2.0 s, echo time (TE) = 30 ms, 32 slices (slice thickness = 4.0 mm, .5 mm skip), and a field of view (FOV) = 200 mm × 200 mm matrix.

Functional data were preprocessed and statistically analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). The images were temporally realigned to the middle slice and spatially realigned to the first in the time series. The images were then coregistered and spatially normalized into standard stereotactic space using the Montreal Neurological Institute (MNI) template. All images were spatially smoothed with an 8 mm full width-half maximum isotropic Gaussian filter.

2.5. fMRI data analysis

Fixed-effects models representing two runs for each participant were used at the individual subject level of analysis and random-effects models were used for group-level regression analyses (SPM5). At the individual level, models were created that represented all event-related task conditions (fear, happy, neutral and scrambled). Each stimulus presentation was modeled as a single event. Data were high-pass filtered. Images identified to correspond with >2 mm of motion were not included in the statistical analysis.

Based on previous studies associating abnormal amygdala function with social processing in WS (Haas et al., 2009; Jawaid, Schmolck, & Schulz, 2008; Martens et al., 2009; Meyer-Lindenberg et al., 2005), we designated the amygdala as an *a priori* region of interest. Two sets of amygdala ROIs were used in this analysis. The first set of amygdala ROIs were delineated on a group averaged T1-weighted spatially normalized high-resolution image based on anatomical landmarks (group averaged ROI) (Mobbs et al., 2004; Reiss et al., 2004). The second set of amygdala ROIs were standardized based on Talairach definitions in standard stereotactic space (standardized ROI) (http://www.fmri.wfubmc.edu). For each set of fMRI analyses, results were considered statistically significant if voxels were identified within both the group averaged ROI and the standardized ROI at corrected ($p < .05$) statistical levels.

To evaluate the extent to which amygdala activation is associated with individual differences in social behaviors in WS, scores for social approach, emotional/empathic sociability and social approach towards strangers were entered separately as regressors into a random-effects regression model. In particular, social approach scores were entered as a regressor using the facial expressions-scrambled images contrast (Fig. 1A), emotional/empathic sociability scores were entered as a regressor using the emotional (fear and happy) facial expressions–neutral facial expressions contrast (Fig. 1B) and social approach towards strangers scores were entered as a regressor using the fearful facial expressions–neutral facial expressions contrast (Fig. 1C). To control for the contribution of age, sex and handedness differences, these variables were also entered in confirmatory analyses as covariates. In order to verify the anatomical specificity of our findings, we also investigated the relationship between social behaviors and activation within two neighboring structures, the hippocampus and parahippocampal gyrus. We used a $p < .05$ statistical threshold (corrected for multiple comparisons within each ROI) for all analyses. For each primary statistical analysis that failed to reach statistical significance we report the R^2 and p value (FWE corrected) of the peak voxel within each ROI.

3. Results

3.1. Behavioral measures

Mean reaction times (981.46 ms) and accuracy rates (72.16%) were calculated for all participants. Reaction time and accuracy rates for all conditions were entered into an ANOVA. There were no statistically significant differences observed between experimental conditions (fearful, happy, neutral and scrambled) in reaction time ($F = .47$, $p = .70$) or accuracy ($F = .08$, $p = .97$). Furthermore, there were no statistically significant differences observed between emotional (fearful and happy) versus neutral face conditions in reaction time ($F = .01$, $p = .93$) or accuracy ($F = .06$, $p = .81$). Reaction times during each experimental condition (fearful, happy, neutral or scrambled) were regressed against each of the sociability measures (indiscriminate sociability, emotional and empathic sociability and social fearlessness) independently. No significant relationships between either reaction time or accuracy and the sociability measures (SISQ) were found.

3.2. Indiscriminate sociability and amygdala response to facial expressions

Social approach scores were regressed against amygdala response to facial (fearful, happy and neutral combined) expressions compared to scrambled images (Fig. 1A). There were no significant positive or negative relationships between social approach scores and either left (group averaged ROI: $R^2 = .33$, $p = .40$; standardized ROI: $R^2 = .27$, $p = .30$) or right (group averaged ROI: $R^2 = .11$, $p = .70$; standardized ROI: $R^2 = .04$, $p = .61$) amygdala response to facial expressions compared to scrambled images. No significant relationships were observed when age, sex and hand-

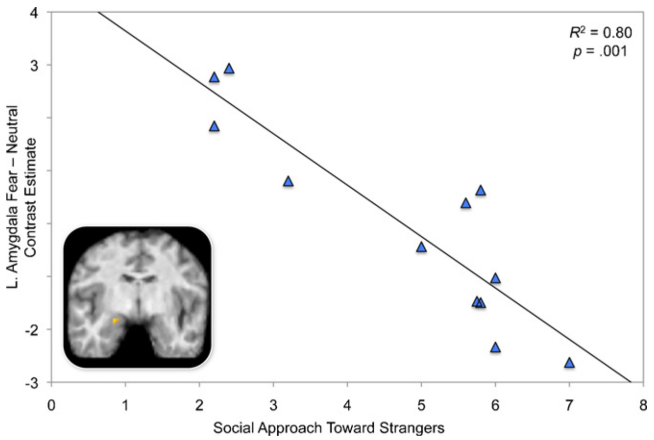

Fig. 3. Individual differences in social approach towards strangers scores associated with left amygdala response to fearful, compared to neutral, facial expressions in WS. Social approach towards strangers scores are plotted on the *x*-axis. Contrast estimates within the left amygdala are plotted on the *y*-axis. Data were extracted from the peak voxel located at MNI coordinates: −20, −6, −6 ($t = 6.41$; $p < .05$ corrected). Cluster found to display a significant correlation is overlaid upon on a coronal slice of a representative WS brain normalized into standard stereotactic space.

edness were entered as covariates. Furthermore, no significant relationships were observed between social approach scores and either hippocampus and parahippocampal gyrus response to facial expressions.

3.3. Emotional/empathic sociability and amygdala response to emotional facial expressions

Emotional/empathic sociability scores were regressed against amygdala response to emotional (both fearful and happy, combined) facial expressions compared to neutral facial expressions (Fig. 1B). There were no significant positive or negative relationships between emotional/empathic sociability scores and either left (group averaged ROI: $R^2 = .52$, $p = .13$; standardized ROI: $R^2 = .51$, $p = .07$) or right (group averaged ROI: $R^2 = .30$, $p = .44$; standardized ROI: $R^2 = .30$, $p = .25$) amygdala response to emotional facial expressions compared to neutral facial expressions. No significant relationships were observed when age, sex and handedness were entered as covariates. Furthermore, no significant relationships were observed between emotional/empathic sociability scores and either hippocampus and parahippocampal gyrus response to emotional facial expressions.

3.4. Social approach towards strangers and amygdala response to fearful facial expressions

Social approach towards strangers scores were regressed against amygdala response to fearful facial expressions compared to neutral facial expressions (Fig. 1C). There was a significant relationship between social approach towards strangers scores and left amygdala response to fearful compared to neutral facial expressions (Fig. 3) (group averaged ROI: MNI coordinates: −20, −6, −6; 47 voxels; $t = 6.41$; $p < .05$ corrected; standardized ROI: MNI coordinates: −24, −6, −14; 13 voxels; $t = 4.70$; $p < .05$ corrected). In particular, the relationship was such that higher scores on social approach towards strangers (greater tendency to approach strangers) were associated with less amygdala response to fearful facial expressions (compared to neutral) (peak voxel: $r = -.89$, $p < .001$).

The relationship between social approach towards strangers and left amygdala response to fearful compared to neutral facial expressions remained significant after controlling for age, sex and handedness (group averaged ROI: $t = 8.16$, $p < .05$ corrected; standardized ROI: $t = 4.43$, $p < .05$ corrected). No significant relationships were observed between social approach towards strangers scores and either hippocampus and parahippocampal gyrus response to fearful facial expressions (compared to neutral).

In order to examine the functional specificity of the relationship between social approach towards strangers and amygdala activation, social approach towards strangers scores were regressed against amygdala response to facial expressions compared to scrambled images and to emotional facial expressions compared to neutral facial expressions. There were no significant positive or negative relationships between social approach towards strangers scores and either left or right amygdala response to facial expressions compared to scrambled images or to emotional (both fearful and happy, combined) facial expressions compared to neutral facial expressions. Controlling for age, sex and handedness did not change this finding.

4. Discussion

WS is characterized by an abnormal social and emotional phenotype (Jarvinen-Pasley et al., 2008; Plesa-Skwerer et al., 2009; Tager-Flusberg, Skwerer, & Joseph, 2006). In this article, we provide support for a model that relates abnormal amygdala response to fear with abnormalities in social approach to strangers in WS. Previous fMRI studies have demonstrated reduced amygdala response to fearful facial expressions in WS, compared to healthy controls (Haas et al., 2009; Meyer-Lindenberg et al., 2005), and have speculated that reduced amygdala response to social fear in WS is a neural construct related to a greater tendency to approach strangers. This study provides direct support to this model by showing that in WS, less amygdala response to fearful facial expressions is associated with a greater tendency to approach strangers.

In this study, we investigated the relationship between social behaviors and amygdala function in WS. The findings of this study advance our understanding of how social and emotional information is processed in WS, but not in healthy controls. One interpretation of the current finding is that the relationship between the tendency to approach strangers and amygdala response to fearful facial expressions also occurs in healthy controls, but that the variation in healthy controls is on a more "normal" scale. Although healthy control participants were not included in this study, insights into the possible differences in social-related amygdala function between those with WS and healthy controls may be gained by comparing the current results to studies relating individual differences in social-related traits and behavior with amygdala response to fear in healthy participants. For example, Canli, Sivers, Whitfield, Gotlib, and Gabrieli (2002) investigated the relationship between extraversion as measured by the NEO-FFI (Costa & McCrae, 1992) and amygdala response to emotional facial expressions and found that individual differences in extraversion were associated with amygdala response to happy facial expressions, but not (positively or negatively) to fearful facial expressions. de Gelder, van de Riet, Grezes, and Denollet (2008) recently reported that no significant relationships were observed between social inhibition as measured by the DS14 (Denollet, 2005) and amygdala response to fearful facial expressions. Lastly, Martens et al. (2009) found that the relationship between amygdala volume and approachability biases was significant in WS, but not in healthy controls. Combined, these studies suggest that the relationship between the tendency to approach strangers and amygdala response to fearful facial expressions may be a neural construct that is specific to WS. However, future fMRI studies that include comparison groups and social behavior assessment will need to be performed to directly test this hypothesis.

We tested three models associating social behavior with amygdala function in WS (Fig. 1). Our findings provide support for a model that relates the tendency to approach strangers with amygdala response to fearful facial expressions in WS (Meyer-Lindenberg et al., 2005, 2006). Consistent with the findings reported here, studies have found that being socially uninhibited or fearless is a critically important feature that defines the WS social phenotype (Bellugi et al., 2007; Bhattacharjee, 2005; Jarvinen-Pasley et al., 2008). Indeed, using the same measure as in this study (SISQ), both Doyle et al. (2004) and Jones et al. (2000) have demonstrated that as compared to healthy controls, those with WS score higher on the social approach towards strangers scale. In addition, studies have demonstrated that WS is associated with an abnormal tendency to approach strangers across various age ranges (Doyle et al., 2004; Gosch & Pankau, 1994; Jones et al., 2000) and across various cultures (Zitzer-Comfort et al., 2007). Abnormalities in the tendency to approach strangers in WS have been speculated to be associated with a reduced response to socially relevant fearful stimuli (Bhattacharjee, 2005; Meyer-Lindenberg et al., 2005). In support of this relationship, Plesa-Skwerer et al. (2006) demonstrated that those with WS exhibit an abnormal ability to perceive negative socially relevant facial and vocal expressions. These studies, along with the current findings, indicate that WS is associated with an abnormal tendency to approach strangers and indicate that a reduced ability to process social fear signals likely contributes to this behavior.

The amygdala is an important brain region for processing social fear (Adolphs, Tranel, & Damasio, 1998; Whalen, 1998) and has been shown to be structurally and functionally abnormal in WS (Haas et al., 2009; Meyer-Lindenberg et al., 2005; Reiss et al., 2004). However, this is the first study to show that individual differences in amygdala response to fear are associated with specific patterns of social behavior in WS. It is important to note that abnormalities within other brain regions such as the frontal lobe may also be associated with the social phenotype in WS (Porter et al., 2007). A potentially relevant clinical inference from this study is that assessing amygdala response to fear in WS may be a useful tool for measuring the efficacy of behavioral intervention techniques in WS. Indeed, clinical reports often cite that a major concern of parents of children with WS, is the potential of harm (i.e. physical and/or sexual exploitation) that may occur as result of their child's overt tendency to approach strangers (Deutsch, Rosse, & Schwartz, 2007; Gosch & Pankau, 1994). The data presented here suggest that those individuals with WS on the "more responsive to fear" side of the spectrum may have learned a different set of social-cognitive strategies throughout development compared to those "less responsive to fear", and therefore, may be less likely to be taken advantage of by strangers. It may also be the case that those on the "less responsive to fear" side of the spectrum may have inherent abnormalities in amygdala structure or function which contribute to altered fear response. Brain-imaging, in particular, may be particularly advantageous (as compared to behavioral assessment alone) in order to examine the efficacy of intervention techniques on alterations in neurobiological mechanisms, such as amygdala function, in WS. Future studies that incorporate brain-imaging with clinical assessment and intervention techniques will need to be conducted to test this hypothesis directly.

The results of this study contribute to a model where abnormal gaze and attention to social stimuli occurs in WS. For example, Mervis et al. (2003) demonstrated that infants with WS spend more time attending to their mothers and strangers as compared to healthy controls. Doherty-Sneddon, Riby, Calderwood, and Ainsworth (2009) recently showed that those with WS exhibit prolonged face gaze under high task demands. The findings of our current study provide a neural correlate to abnormalities of altered attention to negative social stimuli in WS. A logical progression from this research is to combine fMRI with eye tracking during social and emotional processing in WS.

Although this study provides new insights into the neural correlates of social and emotional functioning in WS, it is also limited in several ways. For example, this study only included twelve adult participants with WS. A considerable advantage to utilizing a larger sample size comprised of various age ranges would allow for an investigation of how social and emotional functioning changes throughout development in WS. In addition, including a larger sample size would also allow for comparisons to be made between males and females. In our study however, we undertook procedures in order to demonstrate that independent of other factors such as age, sex or handedness, the relationship between social behavior and amygdala response remained significant at corrected statistical levels. This study is also limited in that only one type of negatively valenced emotional facial expression (fear) was used within the experimental paradigm. One hypothesis is that in WS, emotional and empathic sociability is associated with amygdala response to emotions that convey the need for greater sympathy (i.e. sad). Including other emotions within an experimental paradigm would allow for a more detailed and comprehensive analysis of the relationship between social behaviors and amygdala response to emotions in WS. Lastly, this study is limited in that we used a behavioral measure of sociability that has yet to be normed (SISQ) and we did not collect approachability ratings of each of the facial expressions used as stimuli. We plan to address each of these issues in our future research.

The results of this study indicate that in WS, a greater tendency to approach strangers is associated with less left (but not right) amygdala response to fear. Other studies have reported abnormal bilateral amygdala function (Meyer-Lindenberg et al., 2005) and structure (Reiss et al., 2004), while others have reported just right abnormal amygdala function (Haas et al., 2009) in WS. Martens et al. (2009) reported that the relationship between amygdala *structure* and approachability bias was lateralized to the right amygdala in WS. The current finding that variability of amygdala *function* was lateralized to the left amygdala may indicate that in WS, the right amygdala is more variable in *structure*, while the left amygdala is more variable in *function*. This hypothesis however, will need to be tested directly by combining both imaging approaches.

In conclusion, in this article we provide behavioral and neuroimaging evidence that in WS, reduced amygdala response to fear is associated with a greater tendency to approach strangers. This finding contributes to a social-cognitive model of WS that characterizes this condition to be associated with *social fearlessness*. Continued research of neurodevelopmental conditions such as WS will help elucidate complex relationships among genes, brain development and behavior.

References

Adolphs, R., Tranel, D., & Damasio, A. R. (1998). The human amygdala in social judgment. *Nature*, *393*, 470–474.

Bellugi, U., Adolphs, R., Cassady, C., & Chiles, M. (1999). Towards the neural basis for hypersociability in a genetic syndrome. *Neuroreport*, *10*, 1653–1657.

Bellugi, U., Jarvinen-Pasley, A., Doyle, T. F., Reilly, J., Reiss, A. L., & Korenberg, J. (2007). Affect, social behavior, and the brain in Williams syndrome. *Current Directions in Psychological Science*, *16*, 99–101.

Bhattacharjee, Y. (2005). Friendly faces and unusual minds. *Science*, *310*, 802–804.

Canli, T., Sivers, H., Whitfield, S. L., Gotlib, I. H., & Gabrieli, J. D. (2002). Amygdala response to happy faces as a function of extraversion. *Science*, *296*, 2191.

Costa, P. T., & McCrae, R. R. (1992). *Professional manual of the revised NEO personality inventory and NEO five-factor inventory*. Odessa, FL: PAR Inc.

Davies, M., Udwin, O., & Howlin, P. (1998). Adults with Williams syndrome. Preliminary study of social, emotional and behavioural difficulties. *British Journal of Psychiatry*, *172*, 273–276.

de Gelder, B., van de Riet, W. A., Grezes, J., & Denollet, J. (2008). Decreased differential activity in the amygdala in response to fearful expressions in Type D personality. *Clinical Neurophysiology*, *38*, 163–169.

Denollet, J. (2005). DS14: Standard assessment of negative affectivity, social inhibition, and type D personality. *Psychosomatic Medicine*, *67*, 89–97.

Deutsch, S. I., Rosse, R. B., & Schwartz, B. L. (2007). Williams syndrome: A genetic deletion disorder presenting clues to the biology of sociability and clinical challenges of hypersociability. *CNS Spectrums*, *12*, 903–907.

Doherty-Sneddon, G., Riby, D. M., Calderwood, L., & Ainsworth, L. (2009). Stuck on you: Face-to-face arousal and gaze aversion in Williams syndrome. *Cognitive Neuropsychiatry*, *14*, 510–523.

Doyle, T. F., Bellugi, U., Korenberg, J. R., & Graham, J. (2004). Everybody in the world is my friend" hypersociability in young children with Williams syndrome. *American Journal of Medical Genetics Part A*, *124*, 263–273.

Einfeld, S. L., Tonge, B. J., & Florio, T. (1997). Behavioral and emotional disturbance in individuals with Williams syndrome. *American Journal on Mental Retardation*, *102*, 45–53.

Fidler, D. J., Hepburn, S. L., Most, D. E., Philofsky, A., & Rogers, S. J. (2007). Emotional responsivity in young children with Williams syndrome. *American Journal on Mental Retardation*, *112*, 194–206.

Frigerio, E., Burt, D. M., Gagliardi, C., Cioffi, G., Martelli, S., Perrett, D. I., et al. (2006). Is everybody always my friend? Perception of approachability in Williams syndrome. *Neuropsychologia*, *44*, 254–259.

Gosch, A., & Pankau, R. (1994). Social-emotional and behavioral adjustment in children with Williams–Beuren syndrome. *American Journal of Medical Genetics*, *53*, 335–339.

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*, 1132–1139.

Hoeft, F., Barnea-Goraly, N., Haas, B. W., Golarai, G., Ng, D., Mills, D., et al. (2007). More is not always better: Increased fractional anisotropy of superior longitudinal fasciculus associated with poor visuospatial abilities in Williams syndrome. *Journal of Neuroscience*, *27*, 11960–11965.

Jarvinen-Pasley, A., Bellugi, U., Reilly, J., Mills, D. L., Galaburda, A., Reiss, A. L., et al. (2008). Defining the social phenotype in Williams syndrome: A model for linking gene, the brain, and behavior. *Developmental Psychopathology*, *20*, 1–35.

Jawaid, A., Schmolck, H., & Schulz, P. E. (2008). Hypersociability in Williams syndrome: A role for the amygdala? *Cognitive Neuropsychiatry*, *13*, 338–342.

Jones, W., Bellugi, U., Lai, Z., Chiles, M., Reilly, J., Lincoln, A., et al. (2000). II. Hypersociability in Williams syndrome. *Journal of Cognitive Neuroscience*, *12*(Suppl. 1), 30–46.

Klein-Tasman, B. P., & Mervis, C. B. (2003). Distinctive personality characteristics of 8-, 9-, and 10-year-olds with Williams syndrome. *Developmental Neuropsychology*, *23*, 269–290.

Laws, G., & Bishop, D. (2004). Pragmatic language impairment and social deficits in Williams syndrome: A comparison with Down's syndrome and specific language impairment. *International Journal of Language and Communication Disorders*, *39*, 45–64.

Losh, M., Bellugi, U., Reilly, J., & Anderson, D. (2000). Narrative as a social engagement tool: The excessive use of evaluation in narratives from children with Williams syndrome. *Narrative Inquiry*, *10*, 265–290.

Martens, M. A., Wilson, S. J., Dudgeon, P., & Reutens, D. C. (2009). Approachability and the amygdala: Insights from Williams syndrome. *Neuropsychologia*, *47*, 2446–2453.

Mervis, C. B., & Klein-Tasman, B. P. (2000). Williams syndrome: Cognition, personality, and adaptive behavior. *Mental Retardation and Developmental Disabilities Research Reviews*, *6*, 148–158.

Mervis, C. B., Morris, C. A., Klein-Tasman, B. P., Bertrand, J., Kwitny, S., Appelbaum, L. G., et al. (2003). Attentional characteristics of infants and toddlers with Williams syndrome during triadic interactions. *Devopmental Neuropsychology*, *23*, 243–268.

Meyer-Lindenberg, A., Hariri, A. R., Munoz, K. E., Mervis, C. B., Mattay, V. S., Morris, C. A., et al. (2005). Neural correlates of genetically abnormal social cognition in Williams syndrome. *Nature Neuroscience*, *8*, 991–993.

Meyer-Lindenberg, A., Mervis, C. B., & Berman, K. F. (2006). Neural mechanisms in Williams syndrome: A unique window to genetic influences on cognition and behaviour. *Nature Review Neuroscience*, *7*, 380–393.

Mobbs, D., Garrett, A. S., Menon, V., Rose, F. E., Bellugi, U., & Reiss, A. L. (2004). Anomalous brain activation during face and gaze processing in Williams syndrome. *Neurology*, *62*, 2070–2076.

Plesa-Skwerer, D., Faja, S., Schofield, C., Verbalis, A., & Tager-Flusberg, H. (2006). Perceiving facial and vocal expressions of emotion in individuals with Williams syndrome. *American Journal on Mental Retardardation*, *111*, 15–26.

Plesa-Skwerer, D., Borum, L., Verbalis, A., Schofield, C., Crawford, N., Ciciolla, L., et al. (2009). Autonomic responses to dynamic displays of facial expressions in adolescents and adults with Williams syndrome. *Social Cognitive Affective Neuroscience*, *4*, 93–100.

Porter, M. A., Coltheart, M., & Langdon, R. (2007). The neuropsychological basis of hypersociability in Williams and Down syndrome. *Neuropsychologia*, *45*, 2839–2849.

Reiss, A. L., Eckert, M. A., Rose, F. E., Karchemskiy, A., Kesler, S., Chang, M., et al. (2004). An experiment of nature: Brain anatomy parallels cognition and behavior in Williams syndrome. *Journal of Neuroscience*, *24*, 5009–5015.

Riby, D., & Hancock, P. J. (2009). Looking at movies and cartoons: Eye-tracking evidence from Williams syndrome and autism. *Journal of Intellectual Disability Research*, *53*, 169–181.

Riby, D. M., & Hancock, P. J. (2008). Viewing it differently: Social scene perception in Williams syndrome and autism. *Neuropsychologia*, *46*, 2855–2860.

Tager-Flusberg, H., Skwerer, D. P., & Joseph, R. M. (2006). Model syndromes for investigating social cognitive and affective neuroscience: A comparison of autism and Williams syndrome. *Social Cognitive Affective Neuroscience*, *1*, 175–182.

Tomc, S. A., Williamson, N. K., & Pauli, R. M. (1990). Temperament in Williams syndrome. *American Journal of Medical Genetics*, *36*, 345–352.

Whalen, P. J. (1998). Fear, vigilance, and ambiguity: Initial neuroimaging studies of the human amygdala. *Current Directions in Psychological Science*, *7*, 177–188.

Zitzer-Comfort, C., Doyle, T., Masataka, N., Korenberg, J., & Bellugi, U. (2007). Nature and nurture: Williams syndrome across cultures. *Developmental Science*, *10*, 755–762.