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DEFINING SOCIAL PHENOTYPES IN NEURODEVELOPMENTAL DISORDERS – CONTRIBUTIONS TO SOCIAL COGNITIVE AFFECTIVE NEUROSCIENCE

Topic Editors
Helen Tager-Flusberg
and Daniela Plesa Skwerer

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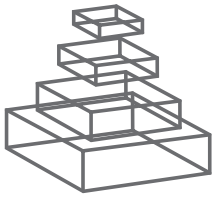

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DEFINING SOCIAL PHENOTYPES IN NEURODEVELOPMENTAL DISORDERS – CONTRIBUTIONS TO SOCIAL COGNITIVE AFFECTIVE NEUROSCIENCE

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Interest in neurodevelopmental disorders as possible windows into the neurogenetic basis of the "social mind" has grown exponentially in the last decades. This interest has been fueled jointly by the development of increasingly refined characterizations of the social-behavioral phenotypes associated with particular syndromes of genetic origin, and by advances in molecular genetics, promising to shed light on genotype-phenotype relationships. Over the last decades, research has made significant progress in refining the phenotypic descriptions of many neurodevelopmental disorders, including those of rare incidence. With advances in this work, it has gradually become apparent that distinctive profiles of social traits are frequently associated with different syndromes. The new awareness of the syndromic specificity of social phenotypes in developmental disorders has raised a set of challenging questions for research and clinical practice. At a theoretical level debates have focused on whether specific disorders provide evidence for or against a modular view of the mind, whether specific cognitive functions may develop along alternative pathways, and whether there are fundamental differences between brain and behavior development in atypical populations. There has been a growing appreciation that the answers to these debates are not as clear-cut as was once thought, because of the highly complex relationships between genes, brain development, environments and behavior that are evident in even the simplest and best understood single gene disorders. Researchers have just recently started to examine systematically the variability in the expression of social cognitive and affective processes in well-defined neurodevelopmental disorders, from the standpoint of an etiology-based approach to atypical development. With investigations focusing on particular aspects of social-behavioral profiles in these populations, such as empathy processes, anxiety, social engagement, social attention

and social cognition, new debates about the nature, causes and interpretation of social impairments have emerged in the literature.

This Frontiers Research Topic issue aims to bring together contributions from researchers whose work addresses these issues by focusing on social cognitive-affective development in populations whose phenotypes include core features that are related to social behavior, such as autism, fragile X syndrome, Williams syndrome, Down syndrome, Prader-Willi syndrome, Turner syndrome, to name a few. This Research Topic issue is open to contributions from research on a variety of other populations with neurodevelopmental disorders, and to researchers from related fields, as it aims to provide an interdisciplinary perspective on the relevance of studying atypical development for advancing our understanding of the 'social mind'. Cross-syndrome comparisons and developmental analyses are especially valuable methodological approaches that could broaden and deepen this discussion.

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EDITORIAL
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Innovative approaches to the study of social phenotypes in neurodevelopmental disorders: an introduction to the research topic

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The field of social-affective neuroscience is growing exponentially, fueled by the availability and widespread use of non-invasive neuroimaging techniques, by advances in molecular genetics and by increasing sophistication in the behavioral characterization of social-affective functioning in both typical and atypical human development. In this context there has been a surge of interest in studying neurodevelopmental disorders (NDDs) as possible windows into the neurogenetic basis of the "social mind". While holding great promise for advancing our understanding of genotype-phenotype relationships, research on neurogenetic disorders has encountered considerable challenges, ranging from the rarity of many NDDs with known genetic etiology and the considerable heterogeneity in phenotypic expressions within syndromes, to the difficulty of designing studies able to take in account the critical role played by developmental and epigenetic processes in shaping phenotypic outcomes. The articles collected in this e-book illustrate several ways in which researchers who study people with NDDs have attempted to overcome these limitations.

The studies selected—both reviews and original research articles—involve populations with NDDs whose phenotypes include core features related to social behavior, primarily autism spectrum disorders (ASD) and Williams syndrome (WS). We chose to focus on these NDDs because they have been viewed as opposite extremes on the social spectrum, and are often still portrayed this way in the popular media. Research findings, by contrast, reveal a much more complex mixture of social-affective strengths and weaknesses in both syndromes, underscoring the need for detailed descriptions of social phenotypes. This ebook brings together a representative sample of research approaches that have begun to uncover these complexities.

In the opening article, Asada and Itakura (2011) review recent research on aspects of social functioning that have received considerable attention in studies of both ASD and WS: face and emotion processing, social cognition, social engagement/motivation, communicative skills and diagnostic assessment outcomes. They discuss behavioral similarities and differences between WS and ASD, their possible developmental origins, and argue for expanding cross-syndrome comparisons to examining the *developmental pathways* leading to distinctive social-affective functioning in ASD and in WS, and to exploring the neural correlates of social-behavioral phenotypes.

Currently, much more is known about the neural substrates of social-behavioral phenotypes in ASD than in WS, but recent neuroimaging studies involving adults with WS are starting to bridge this gap. Haas and Reiss (2012) provide an integrative review of behavioral and neuroimaging studies with WS individuals, discuss the current status of knowledge about the social brain in WS, suggest a framework for understanding how the social brain develops in WS, and propose combining different neuroimaging techniques (fMRI, DTI, functional connectivity analyses) with behavioral tasks and neuropsychological assessments in longitudinal studies as directions for future research.

The two reviews are followed by a selection of original research studies representing various methodological approaches to investigating social phenotypes in NDDs.

The first article by Karmiloff-Smith et al. (2012) presents two case-studies of children with partial genetic deletions in the WS critical region (WSCR)—which encompasses about 28 genes deleted from one copy of chromosome 7: a girl with 24 of 28 genes deleted in the WSCR, and a boy with the opposite profile, i.e., only 4 genes deleted at the telomeric end of the WSCR (including GTF2I, which has been implicated in elevated levels of sociability typical of WS, in prior research). Cases of patients with partial deletions provide unique opportunities to examine the potential contribution of specific genes in the critical region to the unusual social phenotype seen in WS. Results from a large battery of experimental socio-cognitive tasks and standardized assessments revealed a partial WS socio-cognitive profile in the girl, contrasting with a more autistic-like profile in the boy, suggesting that deletion of the telomeric genes alone (including GTF2I) cannot fully account for the hypersociability typical of individuals with WS, and that genetic contributions to phenotypic outcomes involve complex interactions between genes.

The study by Cornish et al. (2012) combines cross-syndrome and prospective-longitudinal designs in examining how attentional profiles impact early socio-cognitive learning in children with WS, children with Down syndrome (DS), and typically developing (TD). These researchers found a complex pattern of *differential relationships* across teacher-report measures of inattention/hyperactivity/social-behavioral profiles and measures of receptive vocabulary and literacy in the WS compared to the DS groups, both concurrently and after 12 months, demonstrating

domain-specific and syndrome-specific influences of attention deficits on socio-cognitive outcomes that appear related to the different genetic abnormalities underlying DS and WS.

Socio-communicative abilities, essential components of social phenotypes, are the focus of two articles, one addressing syndrome-specificity in pragmatic language impairments and their possible relations to molecular genetic variation, the other examining within-syndrome concurrent and longitudinal relations among particular pragmatic language skills.

Losh et al. (2012) conducted detailed cross-syndrome comparisons of performance on measures of pragmatic language ability and socio-cognitive skills in language-matched boys with idiopathic autism, fragile X (FRX) syndrome with autism, FRX without autism, DS and TD. Their behavioral results differentiated children with FRX with and without autism in their performance on both types of measures, sharpening the definition of syndrome-specific social-behavioral profiles in FRX and autism. They further examined possible molecular-genetic correlates of pragmatic language and theory of mind in the group of boys with FXS (disorder caused by 'silencing' of the FMR1 gene), and found that performance on the behavioral measures was correlated with FMR1-related variation, providing evidence for a testable link between genotypic and phenotypic variation.

Using an individual-differences approach and longitudinal design to investigate relations among pragmatic abilities in children with WS across developmental time-points and in relation to expressive vocabulary, John et al. (2012) found that the ability to verbally contribute new information within a social interaction showed stability from preschool to school-age in children with WS, and that differences in this pragmatic skill were predicted by children's ability to engage in triadic joint attention. This is an intriguing finding in light of evidence for atypical relations between early joint attention ability and vocabulary development in children with WS, and underscores the need for more longitudinal, developmental trajectory analyses in defining social phenotypes in NDDs.

van der Fluit et al. (2012) explored relations between performance on a lab-based social perception and social cognition measure—the Social Attribution Task (SAT)—and parent reports of communication and reciprocal social skills in children with WS. They report significant correlations between parent-reported social reciprocity and the typicality of responses on the SAT after taking into account variability in intellectual functioning, suggesting a unique contribution of social cognition deficits to the social reciprocity difficulties of individuals with WS. These authors further analyzed children's responses on the SAT after receiving specific instructions regarding stimuli- interpretation, and revealed a facilitative effect of providing additional structure on social attributions, especially for the children with WS with higher intellectual functioning (e.g., improvements in the quality of the their narratives), finding that may have important implications for developing interventions targeting particular social functioning deficits in this population.

Martens et al. (2012) explored another type of social judgment—attribution of trustworthiness to human faces—in individuals with WS, who have been consistently described as overly friendly and driven to approach strangers. They used a fairly new methodology—computer mouse-tracking—to capture the continuous cognitive dynamics of social-evaluative judgments as they occur in real time. With this technique that allows to visually observe and quantify the competition between responses before the final approach/avoid decision is made, they demonstrated that the WS group showed an approach bias in their increased tendency to initially deviate toward untrustworthy faces, despite discriminating between mild and extreme degrees of trustworthiness in their final response, as the typical controls did. This methodology provides insights into the dynamics of cognitive processing underlying the hypersociability distinctive to the WS social-behavioral phenotype.

Another novel methodological approach to examining a fundamental aspect of social phenotypes—face expertise—was adopted by Parish-Morris et al. (2013). Using eye-tracking technology, these researchers investigated how visual attention to dynamic faces and objects related to face recognition considered on a continuum of ability, in a combined sample of children with ASD and TD controls. They found that visual attention to faces predicted face perception skill in the combined ASD and TD sample after accounting for the effect of age, but that gaze patterns did not vary significantly by diagnostic group. By taking a dimensional approach instead of focusing on group comparisons, these authors were able to capitalize on the heterogeneity of face processing abilities found in both ASD and TD children, and carried out a more direct test of the hypothesized link between social attention and face expertise.

In the final article, Järvinen et al. (2012) describe a multimodal approach to exploring sensitivity to social and non-social visually and aurally presented affective stimuli in individuals with WS and typical controls, as reflected in behavioral responses and autonomic arousal, measured by changes in electrodermal and heart rate activity. Analyses of the psychophysiological measures revealed significant differences in autonomic nervous system (ANS) sensitivity to different categories of affective stimuli and between the visual and auditory domains in individuals with WS—a pattern of ANS reactivity different from that of the typical controls. These findings show that analyses of ANS functioning provide a useful complementary perspective to behavioral paradigms, and a more direct avenue for understanding the neural substrates underlying distinctive patterns of responsiveness to social information found across different disorders.

To conclude, the articles presented in this e-book illustrate a variety of methodological approaches that have the potential to advance our understanding of how phenotypic outcomes emerge from the complex interplay of genetic constraints, environmental conditions and individual experiences, along atypical or typical developmental trajectories. These innovative approaches provide a glimpse into the fascinating new directions in which the study of NDDs may evolve. We hope you will share our enthusiasm for this research and its promises.

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Social phenotypes of autism spectrum disorders and Williams syndrome: similarities and differences

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Autism spectrum disorders (ASD) and Williams syndrome (WS) both are neurodevelopmental disorders, each with a unique social phenotypic pattern. This review article aims to define the similarities and differences between the social phenotypes of ASD and WS. We review studies that have examined individuals with WS using diagnostic assessments such as the Autism Diagnostic Observation Schedule (ADOS), cross-syndrome direct comparison studies, and studies that have individually examined either disorder. We conclude that (1) individuals with these disorders show quite contrasting phenotypes for face processing (i.e., preference to faces and eyes) and sociability (i.e., interest in and motivation to interact with others), and (2) although the ADOS and a direct comparison study on pragmatic language ability suggest more deficits in ASD, individuals with WS are similarly impaired on social cognition and communicative skills. In light of these results, we discuss how cross-syndrome comparisons between ASD and WS can contribute to developmental theory, cognitive neuroscience, and the development and choice of clinical treatments.

Keywords: autism spectrum disorders, Williams syndrome, Autism Diagnostic Observation Schedule, face processing, social cognition, sociability, communication

INTRODUCTION

Autism spectrum disorders (ASD) and Williams syndrome (WS) both are neurodevelopmental disorders. ASD are a group of pervasive developmental disorders usually first seen in childhood, characterized by impairment of social interaction and communication, and by restricted, repetitive, and stereotyped behaviors (American Psychiatric Association, 2000). Approximately half of individuals with ASD have a mild to profound intellectual disability and the other half have cognitive abilities within the normal range of intelligence, while a minority have intelligent quotients well above normal (Joseph, 2011). WS is a rare genetic neurodevelopmental disorder, which is caused by a microdeletion of chromosome 7q11.23 (Ewart et al., 1993). This deletion can be confirmed by fluorescence *in situ* hybridization (FISH) genetic test. Most individuals with WS have a borderline to moderate intellectual disability (Mervis and John, 2010).

Autism spectrum disorders and WS have been described as "opposite" disorders in terms of their social behavior (e.g., Jones et al., 2000). However, there are very few detailed comparisons of the social phenotypes of ASD and WS, including aspects such as social cognition and communicative skills (see Tager-Flusberg et al., 2006 for a review of face recognition and emotion processing with ASD and WS). A better understanding of the similarities and differences between these two disorders could provide insights into gene-brain-behavior relationships. Recently, some genetic studies have begun to identify genes related to both ASD and WS (Feyder et al., 2010; Sanders et al., 2011). Therefore, from the perspective of behavioral genetics, it is important to determine detailed social phenotypes of ASD and WS. In this article, we will review the social phenotypes of these disorders with respect to the following domains: diagnostic assessments, face processing, social cognition, sociability, and communicative skills. After that, we will discuss how a cross-syndrome comparison between ASD and WS can contribute to developmental theory, cognitive neuroscience, and the development and choice of clinical treatments.

DIAGNOSTIC ASSESSMENTS

Earlier studies have reported concurrence of autism and WS (Reiss et al., 1985; Gillberg et al., 1991; Gillberg and Rasmussen, 1994). For example, Gillberg and Rasmussen (1994) provided case reports of four children who had concurrent autism and WS within 60 WS cases registered in their clinic. However, there have been no systematic studies using standardized assessments, and therefore how many individuals with WS would have ASD and how many deficits related to ASD they would have is unknown.

Recently, studies of individuals with ASD and those with WS have been done using the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1999). The ADOS is a structured interaction designed to assess play, reciprocal social interaction, and communication skills, and to diagnose ASD across a range of ages. Lincoln et al. (2007) assessed both children with WS and age- and IQ-equivalent children with autistic disorder using the ADOS Module 1. Among their sample, the DSM-IV (American Psychiatric Association, 1994) criteria placed 20% of the children with WS in the ASD range. Of the 20% group, half met criteria for autistic disorder, and half for pervasive developmental disorder not otherwise specified (PDD-NOS). The ADOS algorithm placed 10% of the children with WS in the ASD range.

Of the 10% group, half met criteria for autism, and half for autism spectrum. They found that many children with WS showed some problems in using pointing (55%), initiating joint attention (50%), and showing an object to another person (65%), but few showed symptoms involving shared enjoyment in interaction (0%), facial expressions directed to others (5%), and quality of social overtures (10%). In addition, they reported that the WS group showed fewer problem behaviors in all of the ADOS items than the autistic disorder group, and a discriminant analysis of ADOS behaviors classified 100% of the cases consistent with their original diagnosis.

On the other hand, Klein-Tasman et al. (2009) emphasized overlaps of ASD with WS, compared with Lincoln et al. (2007). They examined children with WS, autism, PDD-NOS, and mixed etiology non-spectrum developmental disabilities, using the ADOS Module 1. The ADOS algorithm classified the children with WS as autism (10%), autism spectrum (40%), and non-spectrum (50%). Moreover, the WS group showed fewer sociocommunicative abnormalities than the autism group, but about the same as the PDD-NOS group. Klein-Tasman et al. (2009) explained that their results differed from the Lincoln et al. (2007) study because the level of difficulties in their WS sample was more severe than that of Lincoln et al. Also, they did stricter assessments as their sample was well matched with the targets of the ADOS Module 1 compared to those of Lincoln et al. The higher rate at which individuals with WS were categorized as ASD in the Lincoln et al. (2007) and Klein-Tasman et al. (2009) studies might be related to the expanded notion of autism as a spectrum disorder. Klein-Tasman et al. (2007) reported the detailed data of these children with WS.

These studies taken together, using the ADOS, found a certain percentage of individuals with WS showed problem behaviors indicative of ASD, and they were indeed classified as ASD, although the extent of sociocommunicative deficits was less with WS. As Lincoln et al. (2007) pointed out, the quality of some social behaviors (e.g., quality of social overtures) indeed is different between ASD and WS. However, taking into consideration that half of the children with WS were categorized as ASD (Klein-Tasman et al., 2009), we should keep in mind some autistic traits exist within WS. Exploring which social phenotypes are similarly impaired could contribute to understanding the mechanisms of these two disorders. In the following sections, we will take a closer look at similarities and differences between ASD and WS in each social phenotype.

FACE PROCESSING

Most of the direct comparison studies between ASD and WS are with respect to face processing. Riby and Hancock (2008, 2009a,b) examined the way individuals with ASD or WS viewed social stimuli by using eye-tracking techniques. Riby and Hancock (2008) showed photographs of human actors to individuals with autism or WS and typically developing individuals matched for chronological age or non-verbal ability. The individuals with autism spent less time than the control groups viewing actors' faces, but the opposite pattern was found for individuals with WS. A detailed analysis showed that, while individuals with autism spent less time viewing the eyes, individuals with WS spent more time on the eye region than the control groups. Similar results were reported using static cartoon images and movies containing human actors or cartoon characters by Riby and Hancock (2009b). The distinct difference between ASD and WS regarding interest in faces also was found in other types of eye-tracking studies. Riby and Hancock (2009a) examined how individuals with autism or WS viewed scrambled pictures containing faces and pictures of scenes with embedded faces. They reported that individuals with autism showed fewer and shorter fixations on faces, while individuals with WS showed prolonged fixations on faces.

The way that individuals with ASD or WS view faces relates to their face matching skills. Riby et al. (2009) provided individuals with autism or WS unfamiliar face matching tasks, which required the participants to use eyes and mouth cues. Individuals with autism in general performed relatively poorly on these matching tasks, and showed particular deficits when they needed to use the eyes region. On the other hand, individuals with WS showed the typical pattern of performance, with greater accuracy using the eyes than the mouth region.

In addition, Riby et al. (2008) directly compared the face processing skills of ASD and WS individuals. They showed that children and adolescents with WS performed better on processing expressions of emotion (pointing to an image of the person depicting an expression verbalized by the researcher, and matching different faces showing the same expressions) and the direction of eye-gazes (pointing to the face that was looking at the participants, and matching the persons looking in a named direction) than their counterparts with autism matched for non-verbal ability and chronological age. However, Lacroix et al. (2009) reported a different finding with emotion recognition. They used an emotion identification task which required participants to point out the person who expressed a certain emotion among three pictures, and found that children with WS performed worse than children with autism and typically developing children (these groups were matched for verbal mental age).

Taken together, individuals with WS show preference to faces and eyes to a greater extent even than typically developing individuals, while individuals with ASD do not. In addition, although more studies are needed, individuals with WS perform better on some face processing tasks (i.e., matching faces and processing eye-gaze directions) than those with ASD, but mixed findings were obtained regarding emotion recognition.

SOCIAL COGNITION

Social cognitive ability is thought to be one of the most impaired domains of ASD, and considerable effort has been made to research false belief understanding. In Baron-Cohen et al.'s (1985) seminal study, performance on a false belief task was worse by children with autism than by children with Down syndrome or typically developing children. Another study showed that the acquisition of a first-order false belief with autism was considerably delayed. The verbal mental age at which 50% of participants passed the false belief task was 4 years for typically developing children, and 9 years 2 months for those with autism (Happé, 1995). A recent study using the eye-tracking version of the false belief task suggests this difficulty is found even among adults with Asperger syndrome (Senju et al., 2009).

Although there are many studies revealing the impairment of false belief understanding by those with ASD (e.g., Perner et al., 1989; Leekam and Perner, 1991; Leslie and Thaiss, 1992), relatively few studies of this sort have been done regarding WS. Tager-Flusberg and Sullivan (2000) used the false belief task and compared the performance of children with WS to that of age-, IQ-, and language ability-matched children with Prader–Willi syndrome (a genetic disorder resulting from the loss of paternal gene expression at chromosome 15q11-q13), and children with non-specific mental retardation. They showed that the number of WS participants who passed the task was significantly fewer than in the Prader–Willi syndrome group or the non-specific mental retardation group, suggesting impairment of false belief understanding with WS.

The finding of Tager-Flusberg and Sullivan (2000) is partly supported by a subsequent study using a different paradigm. Porter et al. (2008) used a non-verbal picture sequencing task that assesses understanding of false beliefs. They showed that individuals with WS performed worse than mental age-matched typically developing children. However, they also reported that this result was found only for a subgroup of WS, who had better verbal skills compared to their overall mental age.

The impairment of false belief understanding in WS might be surprising given that language promotes false belief understanding (e.g., Farrar and Maag, 2002) and vocabulary skills are not so impaired in WS (e.g., Bellugi et al., 2000; Brock, 2007). However, although data from individuals with ASD support the notion that vocabulary ability correlates with performance on a false belief task (Happé, 1995), we may assume, at least in some developmental disorders, that language is not enough for the acquisition of false belief understanding. This idea is supported by a recent study that revealed individuals with Asperger syndrome could not pass a non-verbal version of a false belief task, even if they have adequate verbal skills and indeed passed a traditional verbal false belief task (Senju et al., 2009). Furthermore, as discussed in the following section on joint attention development, this idea also is consistent with the notion that in ASD and WS, developmental pathways for language and social cognition are unique and relatively unrelated compared with typical development.

Joint attention skills are another aspect of social cognition that has been examined in ASD and WS. Joint attention is thought to be a precursor to complex social cognitive ability (Baron-Cohen, 1995), and there is a relationship between early joint attention behavior and performance on the false belief task (Charman et al., 2000). Deficits in joint attention behaviors with ASD have been found by a number of studies (Curcio, 1978; Mundy et al., 1986; Sigman et al., 1986; Baron-Cohen, 1989).

Mundy et al. (1986) used the Early Social Communication Scales (ESCS; Seibert and Hogan, 1982), a semi-structured observation session to assess a variety of communicative behaviors between the tester and children, with children with autism and children with mental retardation matched for chronological age and mental age. They found that, compared to children with mental retardation, children with autism showed less turn-taking behavior, and less eye contact with the tester. Also, Sigman et al. (1986) observed caregiver-child play interactions and found that, compared to chronological age- and mental age-matched children with mental retardation, children with autism less frequently displayed attention-sharing behaviors such as pointing to an object or showing/giving an object to the caregiver. Curcio (1978) found deficits in joint attention ability with autism, and revealed that non-verbal children with autism showed imperative gestures (i.e., using an adult to obtain an object, event, or activity), but not declarative ones (i.e., using an object to obtain the attention of an adult). Finally, Baron-Cohen (1989) examined comprehension and production of pointing, a key behavior of joint attention, in children with autism. He found that, unlike in control children, those with autism had difficulty both in comprehending and producing declarative pointing.

For individuals with WS, Laing et al. (2002) also used the ESCS (Seibert and Hogan, 1982). They revealed that toddlers with WS more frequently engaged in dyadic, face-to-face interactions, but less did so in triadic joint attention interaction (i.e., an interaction between the child, caregiver, and an external object outside of the face-to-face interaction) than mental age-matched typically developing infants. In addition to using the ESCS, in another experiment they examined comprehension and production of declarative pointing, and found that toddlers with WS had difficulty with both. The discrepancy between imperative and declarative communicative functioning, which was found with individuals with ASD, has not been clearly found with individuals with WS. However, recently, Asada et al. (2010b) found that children with WS clarified what they wanted when they were given the wrong object but not when their requests for objects were just verbally misunderstood, while typically developing children corrected others' misunderstanding in both situations. Therefore, they suggested that the characteristic of ASD, that is, impaired declarative communicative functioning but relatively unimpaired imperative functioning, might be found regarding verbal communications of those with WS.

In addition, it appears there is a similarity in the developmental relationship of joint attention behavior and language production between individuals with ASD and WS. Carpenter et al.'s (2002) cross-sectional study has pointed out that, contrary to both typically developing children and children with developmental delays, there is a possibility that children with autism show a reverse developmental pattern, that is, they may produce referential language before engaging in joint attention behaviors. These findings are surprising, considering that with typical development, words are acquired partly through joint attention behaviors (e.g., Baldwin, 1995; Baron-Cohen et al., 1997). Itoh's (2000) longitudinal study also demonstrated that, although this reverse pattern has been found with other developmental disorders, the gap between the onset of pointing behavior and language was not as long as with individuals with autism (mean gap between onsets: autism, 7.8 months; moderate or severe mental retardation, 3 months). This reverse developmental pattern also was found for WS, and the duration of the gap was almost the same as that for autism. Specifically, Mervis and Bertrand's (1997) longitudinal study found that children with WS followed this reverse pattern, with a gap between onsets of 6 months. A delay in the onset of pointing, which is an early milestone of social cognitive development, compared to that of language, might suggest that verbal communication involving social cognitive ability (e.g., pragmatics) will suffer both with ASD

and WS. Due to differences in research methodology, it is difficult to directly compare these findings. However, at least the developmental pathway of social communication in ASD and WS is similar, and it might be related to later social deficits in both disorders.

In sum, social cognitive ability (i.e., false belief understanding and joint attention) is severely impaired with ASD and also deficient with WS, although there is no direct comparison study between the two disorders regarding the level of difficulties. In addition, the relationship between the development of social cognition and language is unique for both ASD and WS, and it might lead to an atypical social communicative profile.

SOCIABILITY

Studies have examined sociability in ASD and WS. Here, we review the degree to which individuals are interested in or motivated to interact with other people. The biggest difference between ASD and WS occurs in this area. Jones et al. (2000) gave the Salk Institute Sociability Questionnaire to parents of individuals with autism, WS, and Down syndrome, and to parents of typically developing individuals (each group was matched for chronological age). According to a qualitative analysis of the questionnaires, a parent of an individual with autism reported he needed a prompt to say hello and avoided people whenever possible. In contrast, a parent of an individual with WS reported that he was quite happy to meet people and asked a lot of questions. In addition, a qualitative analysis of the questionnaires revealed that individuals with WS were rated as most sociable, individuals with autism were rated as least sociable, and those with Down syndrome and typically developing individuals were rated between WS and autism.

Other studies have reported disinterest and insensitivity to social engagement in ASD. In a retrospective home video analysis, Baranek (1999) reported that children with autism needed more adult prompts to respond after their names were called and more of them showed social touch aversions, compared to children with developmental disabilities and typically developing children. In other home video analysis studies, Osterling and colleagues (Osterling and Dawson, 1994; Osterling et al., 2002) reported that children with ASD looked at others and oriented to their names less frequently than children with mental retardation or typically developing children. In addition, a study using observation of everyday school activities reported that children with autism, on average, initiated communication only three to four times per hour, and spontaneous communication was a relatively rare event for these children (Stone and Caro-Martinez, 1990).

In contrast to ASD, sociable traits of individuals with WS have been reported in various settings. Mervis et al. (2003) observed a scene in a hospital, and found that especially younger children with WS looked intensely at a medical staff, although none of the children in other groups (e.g., children with developmental delay) exhibited this behavior. Similarly, excessive looking at the experimenter by children with WS was reported during play and cognitive assessment (Jones et al., 2000). In addition, Jones et al. (2000) reported that, compared with chronological age-matched typically developing children, children with WS less frequently exhibited negative expressions, and if they occurred, the intensity of them was milder during a task in which the children and their parents were intentionally separated to observe their facial expressions. Recently, Dodd et al. (2010) observed approach behaviors toward strangers in play sessions, and found that pre-school children with WS were more willing to approach others than chronological age- or mental age-matched typically developing children. Only pre-school children with WS initiated interactions with strangers before the strangers noticed them, while none of the typically developing children did so.

Other studies also have found individuals with WS strongly motivated to interact with others. Jones et al. (2000) showed photographs of unfamiliar adult faces to individuals with WS and chronological age- or mental age-matched typically developing individuals, and asked them how much they would like to go up to each person and begin a conversation. Those with WS rated the faces more approachable than both comparison groups. This result was replicated by a study using the same stimuli as Jones et al.'s (2000) study (Martens et al., 2009). Frigerio et al. (2006) found that individuals with WS rated positive faces more approachable and negative faces less approachable than chronological age- or mental age-matched typically developing individuals. Adolphs et al. (2001) used the same approachability task as Jones et al. (2000), and found that high-functioning individuals with autism rated negative faces more approachable than typically developing individuals. Although we should be cautious whether this finding can be generalized to others with ASD, considering that individuals with ASD or WS tend to rate faces more approachable, this finding might indicate social cognitive deficits rather than a motivation to approach others.

Taken together, while individuals with WS have sociable traits and actively want to interact with others, individuals with ASD are relatively insensitive to others' behaviors and are not so interested in engaging socially.

COMMUNICATIVE SKILLS

In this section, we review communicative skills, mainly pragmatic language ability. Pragmatic language ability is broadly defined as the ability to use language in a social context for the purpose of communication. With ASD, pragmatic language is thought to be the most impaired among language abilities, while vocabulary and grammar abilities are relatively less impaired (Tager-Flusberg, 1993, 2000; Fein et al., 1996; Kelly, 2011; Tager-Flusberg et al., 2011). For example, vocabulary ability is a relative strength compared with other language abilities (Fein et al., 1996; Kjelgaard and Tager-Flusberg, 2001; Mottron, 2004). The developmental pathway for grammatical ability in autism follows that of typically developing children, although it is delayed (Tager-Flusberg et al., 1990). Indeed, the level of language abilities is variable across individuals with ASD, but among them pragmatic language ability is universally impaired (Kelly, 2011; Tager-Flusberg et al., 2011).

Some studies on pragmatic language ability have focused on narrative skills of individuals with ASD. Losh and Capps (2003) examined narrative skills of high-functioning children with autism or Asperger syndrome, where they were asked to tell a story while looking at a wordless picture book. Compared with chronological age- and verbal IQ-matched typically developing children, those with autism or Asperger syndrome did not differ in frequency or range of evaluative devices such as intensifiers and

attention-getters. Similarly, it appears that narrative skills are relatively unimpaired also in children with autism who have lower verbal and cognitive abilities (Capps et al., 2000). Capps et al. (2000) examined narrative skills of children with autism, children with developmental delays, and typically developing children using storybook narratives (the groups were matched for language ability). They found several group differences between autistic and typically developing groups; for example, children with autism and children with developmental delays used a more restricted range of evaluative devices such as references to characters' internal states, but not between autistic and developmental delays groups. The fact that narrative skills are relatively unimpaired in these children with ASD might be due to the demand of the storybook narrative task. In this task, individuals did not need to respond to what the listeners said but were asked to speak what they wanted. Therefore, they might not need to recruit impaired skills such as understanding the intention of others.

While previous studies focusing on storybook narratives revealed relatively unimpaired performance by children with ASD, it appears individuals with ASD tend to show more deficits in interactive conversation, where more complex social communicative skills are needed, such as taking into consideration another's state of mind and making conversation relevant to the topic. Paul et al. (2009) observed conversational behaviors with examiners, and found that, compared with chronological age-matched typically developing counterparts, adolescents with Asperger syndrome had more difficulty commenting pertinent to the topic, taking into account the listener's knowledge background, providing the proper amount of information, and maintaining a reciprocal conversational exchange. Also, Capps et al. (1998) observed informal conversation about vacationing, friends, and school, and found that children with autism more often provided no response to comments by the other person, less often gave new and relevant information on an ongoing topic, and more often made bizarre or idiosyncratic responses, compared with language age-matched children with developmental delays.

Similar to ASD, for individuals with WS, vocabulary ability seems to be the strongest area among their language abilities (Brock, 2007). Bellugi et al. (2000) revealed that vocabulary age with WS was significantly better relative to what would be expected from their overall mental age. Unlike an earlier claim that the grammar ability of individuals with WS was intact (Pinker, 1999), the level of grammar ability is below their chronological age, and is thought to be almost on par with their overall mental age (Karmiloff-Smith et al., 1997; Phillips et al., 2004; Brock, 2007). Compared to other aspects of language, studies regarding pragmatic language of individuals with WS are quite few. The debate concerning whether and how much pragmatic language ability with WS is impaired continues. Recently, however, evidence has been accumulating suggesting it is atypical and impaired.

As with ASD, individuals with WS appear to show relative strength in providing narratives, but have deficits in conversation that requires taking others into account. Reilly et al. (2004) analyzed how children with WS told a story while looking at a picture book. They found that, as compared to children with specific language impairment (a developmental disorder diagnosed on the basis of difficulties with language in a child who is otherwise developing normally in the absence of any obvious cause) and typically developing children, children with WS produced a greater proportion of social engagement devices, such as sound effects and audience hookers. Also, Lacroix et al. (2007) found that children and adolescents with WS showed relatively good performance during narrative production, but produced fewer utterances, played a weaker role, and less often satisfied the partner's requests during conversation, compared to mental age-matched typically developing children.

Recent studies have shown that individuals with WS have difficulty in other areas of pragmatic language. Laws and Bishop (2004) used the Children's Communication Checklist (Bishop, 1998) or a modified version of it for parents or teachers of individuals with WS, Down syndrome, or specific language impairment. They revealed that the WS group scored well below the cut-off score at which individuals are categorized as having pragmatic difficulties, while the Down syndrome group and the specific language impairment group both scored at about the cut-off. In addition, the WS group showed difficulties especially with the inappropriate initiation of conversation and the use of stereotyped conversation, and scored lower on these subscales than both the Down syndrome group and the specific language impairment group. Moreover, individuals with WS also have difficulty in making comments relevant to the topic of conversation, sharing their knowledge background with the other person, and repairing communication breakdowns. Stojanovik (2006) investigated the social interaction abilities of children with WS using semi-structured conversations. She found that, compared to children with specific language impairment, children with WS were more likely to produce longer verbal responses, but they were less likely to include new information in their replies. Asada et al. (2010a) found that, while children with WS, in general, showed the same amount of language as verbal mental age-matched typically developing children, children with WS showed less attention-sharing communication. Another study reported that children with WS had difficulty in clarifying what they meant when the listener did not understand them, compared to mental age-matched typically developing children (Asada et al., 2010b). Also, John et al. (2009) reported that the skill of repairing communication breakdowns was related to performance on false belief tasks, suggesting that the pragmatic language deficits with WS relates to their social cognitive ability level.

To the best of our knowledge, there is only one study that directly compares the pragmatic language ability of people with ASD to those with WS. Philofsky et al. (2007) used the Children's Communication Checklist Second Edition (Bishop, 2003) for parents, and directly compared the results for children with ASD with that of children with WS. They found that overall pragmatic functioning, that is, the sum of the pragmatic language subscales of inappropriate initiation, stereotyped language, use of context, and non-verbal communication, was more severely impaired with ASD than with WS. However, the extent of difficulties in the inappropriate initiation of conversation and the use of context did not significantly differ between the groups, although children with WS were rated as more impaired than children with ASD on the inappropriate initiation subscale.

Taken together, the overall language profile of relative strengths (e.g., vocabulary) and weaknesses (e.g., pragmatics) is alike between ASD and WS individuals. Within pragmatic language ability, both individuals with ASD and WS have relatively unimpaired narrative skills, but difficulty with communication involving more social communicative demands, such as taking into account another's mental state and commenting relevant to the topic at hand, although individuals with ASD generally are more impaired than individuals with WS.

The fact that ASD and WS individuals showed similar profiles on communicative skills might be due to social cognitive deficits. Some theorists on pragmatics have claimed that social cognitive skills are needed for pragmatic language comprehension (Sperber and Wilson, 1987), and indeed for both individuals with ASD and WS a direct relationship between pragmatic language ability and social cognitive skills was found in several studies (Happé, 1993; Surian et al., 1996; Hale and Tager-Flusberg, 2005; John et al., 2009). Studies of language acquisition in typical development suggest that vocabulary ability is achieved in several ways, such as inferring speaker intention and use of the mutual exclusivity rule (i.e., every object has only a single label; Markman and Wachtel, 1988; Baldwin, 1995). One study revealed that children with autism learned new words through mutual exclusivity but not by inferring speaker intention (Preissler and Carey, 2005). Therefore, in ASD, vocabulary might be acquired by using only restricted strategies compared with those of typically developing children. We still do not know whether this leads not only to late onset of language but also to later pragmatic language deficits. People might have to learn vocabulary linking to social context where it is used, or learn it while inferring speaker intention in order to use it appropriately. Future studies should explore whether language acquisition without using social cognitive skills would lead to pragmatic language deficits in ASD and WS.

CONCLUSION

Although further cross-syndrome direct comparison studies between ASD and WS are needed, our conclusion regarding the similarities and differences between these two disorders are as follows. (1) Individuals with these disorders show quite contrasting phenotypes with respect to face processing (i.e., preference to faces and eyes) and sociability (i.e., interest in and motivation to interact with others). (2) Although the ADOS and a direct comparison study of pragmatic language ability suggest more deficits with ASD, individuals with WS are similarly impaired with regard to social cognition and communicative skills. Focusing only on sociability, ASD and WS can be viewed as polar opposite disorders (e.g., Jones et al., 2000). However, as we have noted, recent studies have discovered a number of similarities between them, and a growing body of evidence suggests a need to focus on the shared characteristics of these disorders.

There are some limitations of this review. The first has to do with diagnostic categories, levels of functioning, and severity of symptoms. While focusing on a comparison of ASD and WS, we were not able to take a close look at differences according to subcategories on ASD, or to thoroughly consider related levels of functioning (e.g., IQ) or the severity of symptoms. Second is the lack of availability of good comparison group studies focusing on either ASD or WS. That is, some studies recruited only typically developing control group and others used more than one control group, such as individuals with intellectual disabilities without ASD or WS in addition to typically developing controls. Third is the developmental effect of age. According to a report on the anatomical development of the amygdala, compared to typically developing individuals, the volume of the amygdala in individuals with ASD is larger in childhood but not so in adolescence (Schumann et al., 2004). Therefore, symptom expression that relates to amygdala functioning could vary across age ranges due in part to maturation. Recently, research methodology focusing on age-related changes has been utilized for developmental disorders (e.g., Annaz et al., 2009; Thomas et al., 2009). More studies using such a developmental trajectory analysis are needed.

Knowing more about the similarities and differences between these two well-documented disorders could contribute much to both academic and clinical endeavors. First, developmental theory could be more refined. As South et al. (2011) hypothesized, early inadequate motivation for social engagement would lead to less social experience, which subsequently would contribute to eventual later social-perceptual and social-cognitive deficits. For ASD, this seems to be a reasonable hypothesis. On the other hand, individuals with WS display adequate (and even extraordinary) interest in social engagement, and probably have a lot of social experiences. However, as this integrative review indicates, this characteristic of WS does not necessarily lead to functional social skills. One of the clues to this puzzle may come from a computational model proposed by Triesch et al. (2006). According to them, both excessive (as with WS) and scarce (as with ASD) interest in faces should lead to deficits in gaze-following skills, which are an important component of joint attention ability. This is probably because it is difficult to link the partner's eyes (or attention) to the target that the partner is attending to in both cases. That means different characteristics of face processing and sociability between ASD and WS could predict the same outcome: deficits in social cognition. The developmental pathway leading to some difficulty could be different between ASD and WS, even if the difficulty looks similar.

However, other components, which were not examined here, might be related to the social difficulty in ASD and WS. Karmiloff-Smith (2008) proposed that low-level attention deficits could lead to higher-level linguistic and cognitive deficits since saccadic eye movements involve following the partner's focus of attention, which is related to social understanding and language acquisition. There has been evidence on deficits with saccadic eye movement and attentional control both in ASD and WS (Goldberg et al., 2002; Brown et al., 2003; Landry and Bryson, 2004; Van der Geest et al., 2004). Further studies examining the effects on social development both from inside and outside of the social domains will help us to understand how development proceeds in these developmental disorders.

Second, neural substrates of social behavioral phenotypes can be identified. Although brain imaging studies of WS still are few, there is considerable evidence available regarding the neural substrates of social behavioral phenotypes of ASD (see Amaral et al., 2008 for a review). The amygdala is one of the well-studied parts of the brain for both disorders. With ASD, amygdala hypoactivation

was found during the task of interpreting emotional states from viewing eyes (Baron-Cohen et al., 1999) and of processing fearful faces (Ashwin et al., 2007). With WS, the volume of the right amygdala is correlated to how "approachable" participants rate faces in an approachability task (Martens et al., 2009). In addition, Meyer-Lindenberg et al. (2005) revealed that, in contrast to typically developing individuals, those with WS showed heightened activation of the amygdala to non-social stimuli, and less activation to social stimuli. Therefore, atypical amygdala functioning might be related to social cognitive impairment and aberrant sociability for both disorders. Given that ASD and WS have similar social cognitive deficits but different aspects of sociability, the amygdala might be differentially impaired or other neural domains linked to the amygdala might be related to these two disorders. However, we should keep in mind that aspects of amygdala functioning still are under debate (e.g., arousal rather than social cognition; South et al., 2011). For ASD, the exploration of neural substrates for impaired social behavioral phenotypes is relatively advanced (e.g., superior temporal sulcus for gaze processing, Pelphrey et al., 2005; medial prefrontal cortex, superior temporal sulcus, and temporal poles for attributing mental states, Castelli et al., 2002). Future studies should examine brain functioning in these areas regarding WS.

Third, intervention techniques could be shared. The impaired social phenotypes that this article revealed both in ASD and WS are with respect to social cognitive and communicative skills. Indeed, many of the intervention techniques for ASD focus on these same areas (e.g., social skills training; see Howlin and Charman, 2011 for a review). As Klein-Tasman et al. (2007) pointed out, intervention techniques for ASD were developed to improve behavioral phenotypes, rather than to address the biological causes of disorders, and therefore these techniques should be helpful for other developmental disorders with similar difficulties. Considering that few interventions have been developed for WS, it might be helpful for clinicians and parents to consider these techniques for WS. However, rigorous trials to test the effectiveness of these techniques for ASD still are few in number (Howlin and Charman, 2011). The determination of the effectiveness of each technique for each disorder is necessary and very important.

Finally, this past decade has seen dramatic improvements in the study of developmental disorders. Hereafter, cross-syndrome studies focusing on social phenotypes other than face processing and brain imaging studies will be beneficial in determining the characteristics of these developmental disorders. We believe such attempts will make further contributions to understanding each disorder, and what intervention techniques might be effective for clinical treatments.

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Social brain development in Williams syndrome: the current status and directions for future research

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Williams syndrome (WS) is a neurodevelopmental condition that occurs as a result of a contiguous deletion of ∼26–28 genes on chromosome 7q11.23. WS is often associated with a distinctive social phenotype characterized by an increased affinity toward processing faces, reduced sensitivity to fear related social stimuli and a reduced ability to form concrete social relationships. Understanding the biological mechanisms that underlie the social phenotype in WS may elucidate genetic and neural factors influencing the typical development of the social brain. In this article, we review available studies investigating the social phenotype of WS throughout development and neuroimaging studies investigating brain structure and function as related to social and emotional functioning in this condition. This review makes an important contribution by highlighting several neuro-behavioral mechanisms that may be a cause or a consequence of atypical social development in WS. In particular, we discuss how distinctive social behaviors in WS may be associated with alterations or delays in the cortical representation of faces, connectivity within the ventral stream, structure and function of the amygdala and how long- and short-range connections develop within the brain. We integrate research on typical brain development and from existing behavioral and neuroimaging research on WS. We conclude with a discussion of how genetic and environmental factors might interact to influence social brain development in WS and how future neuroimaging and behavioral research can further elucidate social brain development in WS. Lastly, we describe how ongoing studies may translate to improved social developmental outcomes for individuals with WS.

Keywords: Williams syndrome, development, social, emotion, review

INTRODUCTION

Williams syndrome (WS) is a neurodevelopmental condition that occurs in ∼1 in every 8,000 live births and arises as a result of a contiguous deletion of ∼26–28 genes on chromosome 7q11.23. Individuals with WS are characterized by a compelling psychological phenotype comprised of relative strengths and weaknesses across multiple cognitive domains and with a distinctive pattern of social behavior (Martens et al., 2008). One of the most compelling aspects of the WS social phenotype is an increased appetitive drive toward social interaction (Jarvinen-Pasley et al., 2008). People with WS will often approach others, including strangers, with little to no regard of potential negative consequences. In terms of development, many parents and caregivers of children with WS are challenged by the task of teaching their children to behave in socially appropriate ways. Studies designed to elucidate the trajectory of social functioning and brain development in WS are a critical step toward the design and implementation of targeted intervention techniques that promote healthy social development in affected individuals and may elucidate important genetic and neural factors influencing the normal development of the social brain.

The goal of this article is to present a framework for how the social brain develops in WS. We will review empirical evidence characterizing the social phenotype throughout development and evidence characterizing alterations of brain regions important for social functioning in WS. We will discuss how atypical brain development may relate to distinctive social behaviors in WS. Lastly, we will discuss ongoing and future research on social brain development in WS and discuss the value of cross-disciplinary research in terms of elucidating how the social brain develops in WS.

SOCIAL PHENOTYPE AND THE SOCIAL BRAIN IN WILLIAMS SYNDROME

The social phenotype associated with WS is in stark contrast to social phenotypes associated with many other neurodevelopmental conditions. For example, while individuals with autism or fragile X tend to be "socially distant" or averse to approaching others (Reiss and Hall, 2007), individuals with WS are often described as being "hypersocial." Approaching strangers, fixating on faces, and speaking in close proximity to others, are all characteristic behaviors associated with WS. One of the earliest published reports on WS described a group of WS patients as having the "same kind of friendly nature" and that "they love everyone, are loved by everyone, and are very charming" (Beuren et al., 1962). The apparent increased sociability often ascribed to people with WS has motivated the design of many studies focused on elucidating the social phenotype of WS.

PERSONALITY, TEMPERAMENT, AND SOCIABILITY IN WILLIAMS SYNDROME

Approaches to investigating social functioning in WS include performing observational research and quantifying the manner in which parents of children with WS characterize their child's social behavior. Evidence from observational research indicates that children with WS make more efforts to socially engage others as compared to children with autism (Lincoln et al., 2007), display fewer socio-communicative abnormalities than children with autism (Klein-Tasman et al., 2009) and are more willing to approach strangers relative to typically developing (TD) controls (Dodd et al., 2010). These studies suggest that in naturalistic settings, children with WS display a distinctive pattern of social behavior characterized by an increased affinity toward social interaction relative to children who are autistic or TD.

Many studies have demonstrated that parents of children with WS rate their child as being more "overtly social" as compared to parents of TD children. For example, parents rate children with WS as displaying higher "intensity" of social approach relative to parents of TD children (Tomc et al., 1990). These parents also rate their child with WS as being less reserved around strangers (Gosch and Pankau, 1994) and more "globally social" (Doyle et al., 2004; Zitzer-Comfort et al., 2007) relative to parents of TD children. Together, these studies indicate that children with WS are consistently characterized as being more likely to socially interact with others as compared to children with other neurodevelopmental conditions and those who are TD.

FACE PROCESSING IN WILLIAMS SYNDROME

Individuals with WS tend to process faces atypically. Specifically, people with WS tend to focus more attention on faces and socially relevant cues (e.g., eyes) as compared to controls. As evidenced by eye-tracking, people with WS fixate on faces longer (Riby and Hancock, 2008, 2009) and are slower to disengage their gaze once fixated on eyes (Porter et al., 2010) or a face (Riby et al., 2010) relative to controls. Lastly, observational research during social interactions has shown that children with WS tend to hold gaze on faces for a prolonged period of time relative to TD children (Mervis et al., 2003; Doherty-Sneddon et al., 2009). Together, these findings suggest that an increased tendency to focus on faces may be associated with the overt, highly motivated, drive toward social interaction commonly observed in WS.

Although individuals with WS may have a spared (or even heightened) affinity toward processing faces, the manner in which the cognitive mechanisms supporting face recognition develop in WS is currently not well understood. For example, there is evidence indicating that individuals with WS tend to recognize and distinguish faces based on individual features comprising a face (such as the eyes and the mouth, indicating feature based processing), while TD individuals tend to recognize and distinguish faces based on the configuration of the entire face (i.e., the overall arrangement of the features of the face or "configural" based processing) (Deruelle et al., 1999; Karmiloff-Smith et al., 2004; Isaac and Lincoln, 2011). Conversely, there are also reports of spared configural or holistic face processing in WS (Tager-Flusberg et al., 2003; Deruelle et al., 2006; Annaz et al., 2009). Together, these findings support the hypothesis that development of face processing in WS follows an atypical trajectory (Leonard et al., 2011). However it is currently unclear if the developmental trajectory of face processing in WS is better described as "deviant," "delayed" or a combination of both as compared to that of the TD trajectory.

EMOTION PROCESSING IN WILLIAMS SYNDROME

Individuals with WS tend to process emotions atypically. In particular, those with WS are less able to detect social fear signals as compared to controls. Plesa-Skwerer et al. (2006) showed that individuals with WS are less able to perceive negative emotions conveyed through facial expressions and voices relative to controls. Furthermore, those with WS are less accurate in detecting the presence of angry faces during a visual search task (Santos et al., 2010) and are less aroused in response to angry faces (Plesa-Skwerer et al., 2009) or scenes (Plesa-Skwerer et al., 2011) relative to controls. These studies suggest that the reduced ability to detect social threat signals may be an important factor related to the tendency to uninhibitedly approach strangers in WS.

Recently, evidence has emerged that persons with WS exhibit a bias toward processing positive emotional facial expressions. For example, those with WS rate happy facial expressions as more approachable (relative to other emotions), as compared to controls (Frigerio et al., 2006). Additionally, individuals with WS tend to focus a greater amount of attention on happy faces (relative to other emotions) as compared to controls (Dodd and Porter, 2010). Combined, these studies indicate that WS is associated with a reduced ability to detect social threat signals (e.g., fear and angry faces) and an increased bias toward processing positive social signals (e.g., happy faces) and support the hypothesis that WS is associated with atypical or delayed development of emotion processing.

BEHAVIORAL INHIBITION

Williams syndrome is associated with poor social inhibition that may in part in be related to deficits in inhibition in general (Porter et al., 2007). For example, individuals with WS may approach others such as strangers due to a reduced ability to inhibit the urge to socially interact with others. Behavioral studies have shown that individuals with WS typically commit more errors during response inhibition tasks as compared to controls (Menghini et al., 2010) and also experience more difficulties inhibiting their emotions as compared to controls (Mervis and Klein-Tasman, 2000). In addition, deficits in response inhibition have been shown in children with WS as young as 18 months of age (Cornish et al., 2007). Recent evidence however, indicates that deficits in response inhibition may be primarily related to IQ as opposed to social functioning in WS (Capitao et al., 2011a) suggesting that atypical social behavior may be, in part, secondary to cognitive impairments. Combined, problems in inhibiting behavior and emotions are characteristics of the WS phenotype and may be related to the distinctive pattern of social behavior in this condition.

HIGHER ORDER SOCIAL–COGNITIVE FUNCTIONS

Individuals with WS often demonstrate difficulties in higher order social-cognitive functions manifested by atypical non-verbal communication, imagination, and problems in understanding the mental states of others (i.e., theory of mind). For example, while

playing in a group, children with WS exhibit less spontaneous functional play and imaginary play compared to TD children (Papaeliou et al., 2011). Those with WS are less accurate in labeling emotions from brief dynamic facial displays (Skwerer et al., 2006) and are less accurate when tested with several types of theory of mind tasks (Porter et al., 2008; Santos and Deruelle, 2009). Tager-Flusberg and Sullivan (2000) argued that the social-cognitive component of theory of mind is compromised in WS while the social perceptual component of theory of mind is spared. In summary, there is considerable evidence that WS is associated with difficulties in processing complex social-cognitive information and that social-cognitive development is either atypical and/or delayed in WS.

EARLY CHILDHOOD

Children with WS exhibit a distinctive pattern of social behavior during early development. Infants and young children with WS (ages 8–43 months) exhibit greater amounts of extended, intense gaze toward the faces of others relative to controls (Mervis et al., 2003). Children with WS (age from 1 year, 1 month to 12 years, 10 months) consistently score higher on several measures of sociability (parental ratings) as compared to controls (Doyle et al., 2004). Lastly, as measured by the Multidimensional Personality Questionnaire-Parent Version (Tellegen, 1985), children with WS (ages 8–10 years) are characterized as being relatively more gregarious, people-oriented, and sensitive as compared to controls (Klein-Tasman and Mervis, 2003). Combined, these studies demonstrate that from an early age (8 months), children with WS exhibit behaviors consistent with the tendency to be more driven to socially interact as compared to controls.

SUMMARY: SOCIAL PHENOTYPE OF WILLIAMS SYNDROME

Empirical research has shown that several aspects of social functioning are atypical during development in WS (**Table 1**). Specifically, WS is associated with atypical (i) personality: high gregariousness, intensity, and global sociability (Tomc et al., 1990; Klein-Tasman and Mervis, 2003; Doyle et al., 2004), (ii) face processing: increased focus on faces and eyes (Riby and Hancock, 2008, 2009), (iii) emotion processing: reduced ability to detect social threat signals (Plesa-Skwerer et al., 2006, 2009; Santos et al., 2010) and increased attentional bias toward positive social signals (Dodd and Porter, 2010), (iv) reduced ability to inhibit behavior (Porter et al., 2007; Menghini et al., 2010) and emotions (Mervis and Klein-Tasman, 2000), and (v) reduced ability to understand the mental states of others (Tager-Flusberg and Sullivan, 2000; Porter et al., 2008; Santos and Deruelle, 2009). The a distinctive pattern of social behavior in WS is present during very early stages of development (as early as 8 months; Mervis et al., 2003) and is persistent throughout adulthood (Elison et al., 2010).

Table 1 | Summary of social phenotype of WS.

Aspect of social function	Abnormality in WS
Personality	High gregariousness, intensity and global sociability
Face processing	Increased focus on faces and eyes
Emotion processing	Reduced ability to detect social threat signals
	Increased attentional bias toward positive social signals
Inhibition	Increased number of errors during response inhibition tasks
	Reduced ability to regulate emotions
Higher order social cognition	Reduced ability to understand the mental states of others

THE SOCIAL BRAIN IN WILLIAMS SYNDROME

Williams syndrome is associated with atypical functional anatomy of brain regions important for social behavior and emotional processing. Considerable evidence derived from brain imaging research indicates that alterations of the fusiform face area (FFA), amygdala and connections within the brain are important neural substrates associated with the social phenotype in WS. More specifically, alterations of the FFA are likely associated with atypical face processing, alterations of the amygdala may be linked to atypical emotion processing and altered connectivity within the ventral stream and frontostriatal pathway may be linked to distinctive patterns of social behavior and emotion processing. In the following section, we will review studies that have investigated the neural substrates of social behavior and emotion processing in WS.

BRAIN REGIONS INVOLVED IN FACE PROCESSING

Williams syndrome is associated with altered structure and function within brain regions important for face processing. The fusiform gyrus is located on the inferior medial surface of the temporal lobe and is functionally involved in object and face recognition. Magnetic resonance imaging (MRI) studies have demonstrated that the structure of the fusiform gyrus is atypical in WS. For example, using a 3D cortical surface modeling approach, Thompson et al. (2005) demonstrated that adults with WS exhibit greater cortical gray matter thickness of the fusiform gyrus relative to TD adults. Reiss et al. (2004) used a voxel based morphometry (VBM) approach to show greater gray matter density within the fusiform gyrus in adults WS as compared to TD controls. Campbell et al. (2009) also used VBM to show reduced gray matter volume in the left fusiform and increased gray matter volume in the right fusiform in children and adolescents with WS (age range: 8–16 years) relative to TD children and adolescents. Together, these studies indicate that atypical structure of the fusiform gyrus may be an important neural substrate associated with the distinctive pattern of face processing in WS.

Within the fusiform gyrus, the FFA is a highly specialized region for face recognition (Kanwisher et al., 1997). In TD individuals, activation within the FFA is consistently greater when responding to faces vs. other types of stimuli such as houses (Kanwisher and Yovel, 2006) and is correlated with the ability to detect the presence of faces (Grill-Spector et al., 2004). One way to elucidate how the FFA functions in atypical and typical populations is to use functional magnetic resonance imaging (fMRI). fMRI is a particularly advantageous tool to investigate the extent to which brain regions are responsive during the processing of specific types of stimuli. Mobbs et al. (2004) used fMRI and demonstrated that individuals with WS exhibit greater activation within the fusiform gyrus when

responding to faces relative to TD controls. In another study from our laboratory, we used fMRI and a face processing task to quantify the volume of the FFA within a group of adults with WS relative to a TD control group (**Figure 1**; Golarai et al., 2010a). The results of this study showed that although individuals with WS exhibit a reduced total volume of the fusiform gyrus (structurally defined), the volume of the FFA (functionally defined) is larger in WS relative to TD controls. Additionally, we found that the functional volume of the FFA is correlated with face recognition accuracy in WS. Recently, O'Hearn et al. (2011) also reported that the FFA is larger in WS relative to controls and showed that the cortical representation of other types of stimuli (e.g., houses) is relatively smaller in WS.

BRAIN REGIONS INVOLVED IN EMOTION PROCESSING

Williams syndrome is associated with atypical structure and function within brain regions important for processing emotions. The amygdala is located within the medial temporal lobe and is involved in assessing the emotional salience of stimuli within the environment (Aggleton, 2000). MRI studies have shown that the volume of the amygdala is greater in WS relative to controls. For example, using a manual delineation, region of interest (ROI) approach Reiss et al. (2004) demonstrated that the total gray matter volume of the amygdala (after controlling for total brain volume) is greater in adults with WS relative to TD controls. Other studies have used similar approaches and have similarly reported greater amygdala volumes in WS relative to controls (Martens et al., 2009; Capitao et al., 2011b). Furthermore, the results of a combined structural MRI and behavioral study by Martens et al. (2009) demonstrated that the volume of the amygdala is correlated with approachability ratings of emotional facial expressions in WS. These findings suggest that an enlarged volume of the amygdala may be associated with atypical emotion processing in WS.

In addition to structural alterations, WS is associated with atypical amygdala response to social-emotional stimuli. Meyer-Lindenberg et al. (2005) used fMRI to show that adults with WS exhibit a reduced, or blunted, amygdala response to fearful facial expressions as compared to TD controls. Our group has replicated this finding (Haas et al., 2009; Mimura et al., 2010). In addition, we demonstrated that amygdala response to fearful facial expressions is correlated with the tendency to approach strangers in WS (Haas et al., 2010; **Figure 2**).

Interestingly, in contrast to the pattern of amygdala response to fearful facial expressions, individuals with WS exhibit greater amygdala response to happy facial expressions relative to controls (Haas et al., 2009). Combined, these findings suggest that reduced amygdala response to fearful facial expressions may be a neural substrate associated with the tendency to uninhibitedly (or

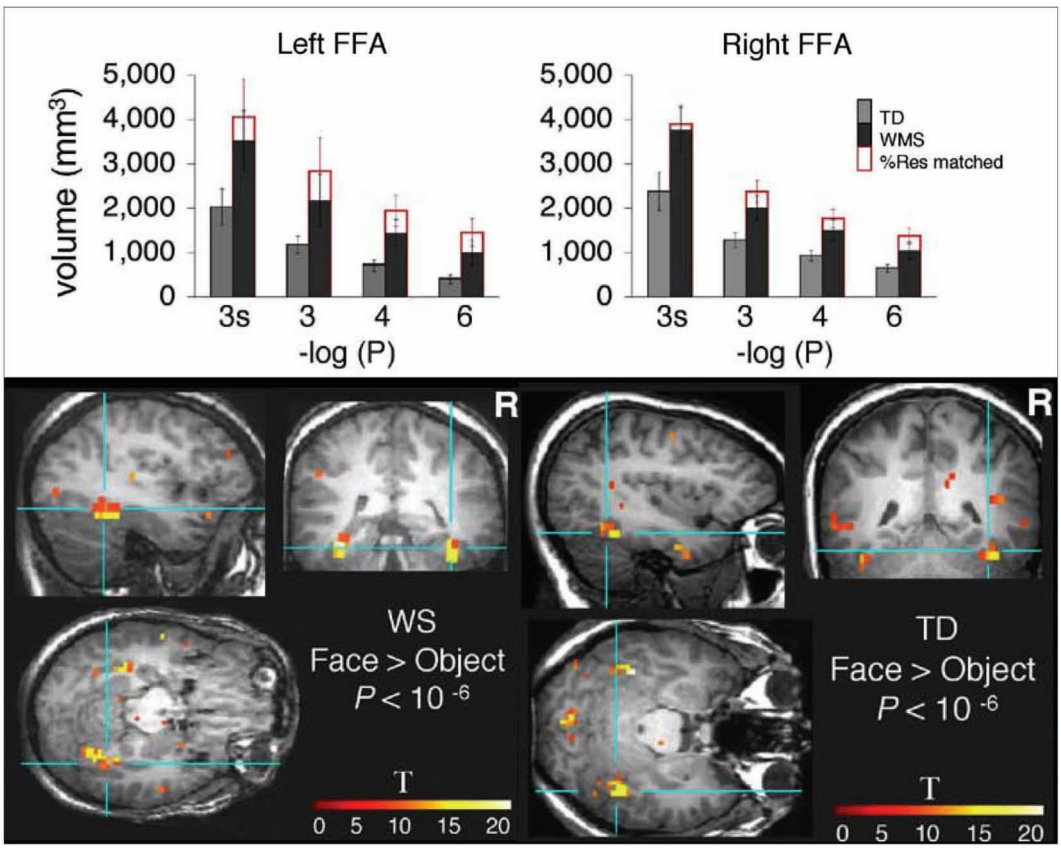

FIGURE 1 | The FFA is larger in WS (Williams syndrome) compared to TD (typically developing) adults. Upper panel: Bars represent the volume of the FFA (functionally defined) as defined by various statistical thresholds and smoothing techniques. Images presented in the lower panel display an FFA defined on a WS brain (left) and a TD brain (right). Adapted from Golarai et al. (2010a) the Journal of Neuroscience.

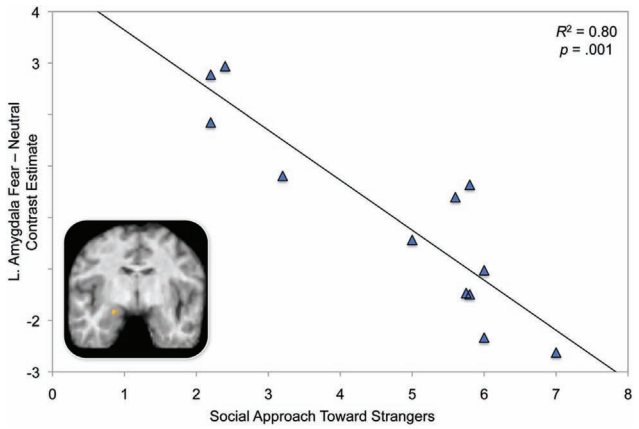

FIGURE 2 | Individual differences in social behavior (Social Approach Toward Strangers scores) associated with left amygdala response to fearful, compared to neutral, facial expressions in WS. Tendency to approach strangers (as rated by a caregiver) are plotted on the x-axis. Contrast estimates within the left amygdala are plotted on the y-axis. Adapted from Haas et al. (2010) Neuropsychologia.

"fearlessly") approach strangers in WS, while increased amygdala response to happy facial expressions may be a neural substrate associated with the tendency to be more "driven" (or motivated) to approach others.

BRAIN CONNECTIONS INVOLVED IN FACE AND EMOTION PROCESSING

Williams syndrome is associated with atypical anatomical and functional connectivity between brain regions important for face and emotion processing. Sarpal et al. (2008) demonstrated that when processing facial expressions, individuals with WS exhibit less functional connectivity between the FFA and amygdala relative to controls. Our group recently used a diffusion tensor imaging (DTI) approach to show that individuals with WS exhibit an increase in the volume, fractional anisotropy, and fiber density index of white matter fibers projecting through the fusiform gyrus in WS relative to controls (Haas et al., 2012; **Figure 3**). In addition, Mobbs et al. (2007) showed that during a response inhibition task, individuals with WS fail to recruit frontostriatal circuitry implicated in inhibition. This finding suggests that WS is associated with altered connectivity between striatal areas and prefrontal cortices. Together, these results support the hypothesis that the neural pathways that serve to connect brain regions important for social, emotional and inhibitory processing are atypical in WS.

SUMMARY: THE SOCIAL BRAIN IN WILLIAMS SYNDROME

Neuroimaging research has elucidated how several neural substrates may be associated with the distinctive social phenotype in WS (**Table 2**). Specifically, WS is associated with: (i) altered structure of the fusiform gyrus (Reiss et al., 2004; Thompson et al., 2005; Campbell et al., 2009), (ii) larger volume of the FFA (Golarai et al., 2010a; O'Hearn et al., 2011), (iii) larger amygdala volume (Reiss et al., 2004; Martens et al., 2009; Capitao et al., 2011b), (iv) altered amygdala function: reduced response to fearful facial expressions (Meyer-Lindenberg et al., 2005; Haas et al., 2009) and heightened response to happy facial expressions (Haas et al., 2009), and (v) altered connectivity associated with the fusiform cortex and amygdala (Sarpal et al., 2008; Haas et al., 2012) and within frontostriatal pathways (Mobbs et al., 2007). Together, these findings demonstrate that in adulthood, WS is characterized by altered functional anatomy of brain regions important for social behavior and emotion processing. In addition, these studies provide support to the hypothesis that the development of neural circuitry important for social and emotional functioning is atypical in WS.

SOCIAL BRAIN DEVELOPMENT IN WILLIAMS SYNDROME

Integrating findings from behavioral and neuroimaging research can potentially provide insight as to how altered or delayed brain development contributes to, or results from atypical social behavior in WS. Behavioral research has demonstrated that distinctive patterns of social behavior and emotion processing exist early in childhood in WS (Mervis et al., 2003) and that the acquisition of social-emotional skills follows an atypical trajectory in affected individuals (Annaz et al., 2009; Leonard et al., 2011). Neuroimaging research has demonstrated that during adulthood, the functional anatomy of brain regions important for social-emotional processing is altered in WS (Reiss et al., 2004; Haas et al., 2009; Martens et al., 2009; Golarai et al., 2010a). In the following section we will discuss how the social brain may exhibit an atypical or delayed developmental pattern in WS. We will draw evidence from studies reviewed within the previous section of this article and from research on social brain development in healthy populations.

CORTICAL REPRESENTATION OF FACES

During typical development, the FFA grows in volume throughout childhood (Golarai et al., 2007; Peelen et al., 2009) and late adolescence (Golarai et al., 2010b), ultimately stabilizing in volume in early adulthood. The trajectory of FFA development is typically more prolonged as compared to the development of ventral stream areas allotted to processing other types of visual stimuli (Peelen et al., 2009; Golarai et al., 2010b). Increased FFA volume during development is associated with improved face recognition memory performance (Golarai et al., 2007, 2010b). In terms of the cognitive mechanisms underlying face processing, the development of feature based face recognition occurs more rapidly than configural based face recognition (Mondloch et al., 2002) and fMRI research has demonstrated separate networks within the fusiform gyrus specialized for these different face processing mechanisms (Maurer et al., 2007). Overall, typical development of the cortical representation for processing faces is a dynamic process that extends through late adolescence and is associated with dissociable cognitive-behavioral aspects of face processing (i.e., featural vs. configural based).

As we have discussed, adults with WS exhibit a disproportionately greater area of the fusiform gyrus allotted to processing faces (FFA), as compared to the fusiform region allotted to processing other types of visual stimuli (Golarai et al., 2010a; O'Hearn et al., 2011). Further, one might speculate that, during childhood, fusiform components specialized for specific aspects of face processing (i.e., featural vs. configurual) may develop more rapidly or be spared relative to fusiform regions specialized for other aspects of face processing in WS. The differential development of

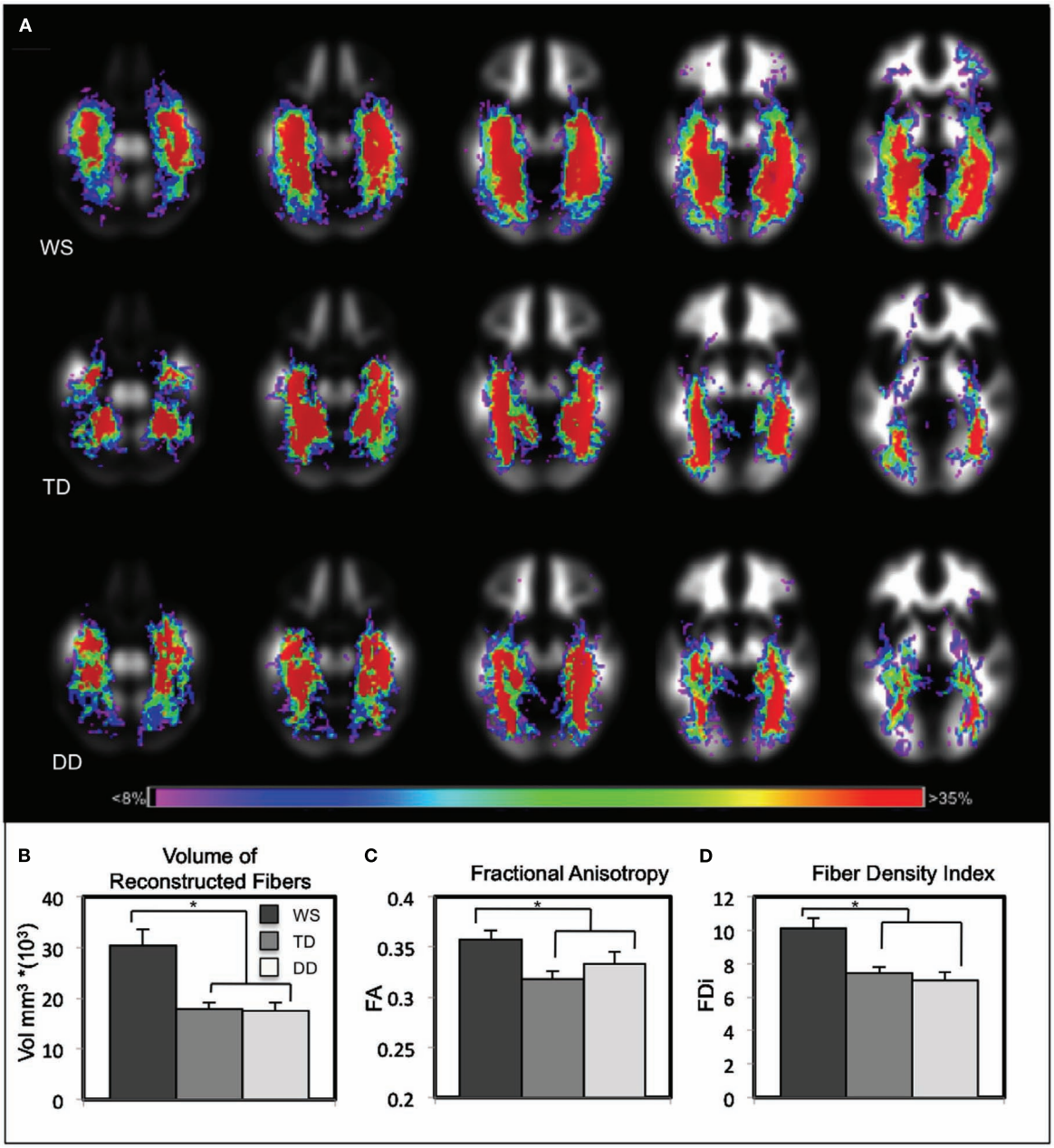

FIGURE 3 | Reconstructed white matter fibers projecting through the fusiform gyrus in the WS (Williams syndrome), TD (typically developing), and DD (developmentally delayed) groups. Color scale within probabilistic maps **(A)** corresponds to the relative probability of reconstructed fibers being present at each location, within each group. Plots of macro- [**(B)** volume of reconstructed fibers] and micro- [**(C)** fractional anisotropy and **(D)** fiber density index] for fibers projecting through the fusiform gyrus in WS, TD and DD participants. Vol mm^3, volume in millimeters; FA, fractional anisotropy; FDi, fiber density index; *$p < 0.05$. Error bars represent standard error from the mean. Adapted from Haas et al. (2012) Genes, Brain, and Behavior.

cortical areas within the fusiform gyrus in WS may be a primary or secondary neural substrate associated with increased attention to faces (Riby and Hancock, 2008, 2009) and a reduced ability to identify objects and places based on visuo-spatial cues (Paul et al., 2002; Landau et al., 2006; Lakusta et al., 2010).

VENTRAL STREAM CONNECTIVITY

In typical development, white matter develops rapidly throughout the first 2 years of life (Gao et al., 2009) and continues to develop throughout adulthood (Kochunov et al., 2010). Studies using DTI have demonstrated that major white matter pathways within the brain exhibit differential rates of development (Barnea-Goraly et al., 2005; Eluvathingal et al., 2007; Kochunov et al., 2010). For example, the results of a DTI study by Kochunov et al. (2010) indicated that the fronto-occipital tract (part of the inferior fronto-occipital fasciculus: IFOF) matures at a faster rate relative to the superior longitudinal fasciculus (SLF). Functionally, the IFOF is an important pathway related to the ability to process

Table 2 | Summary of neural substrates of social-emotional functioning in WS.

Neural substrate	Abnormality in WS
Structure of fusiform gyrus	Increased gray matter thickness Increased gray matter volume in the right fusiform
Volume of fusiform face area (FFA)	Increased functionally defined volume
Amygdala structure	Increased volume
Amygdala function	Reduced response to fearful faces Increased response to happy faces
Connectivity	Reduced functional connectivity between the FFA and amygdala Increased volume of white matter fibers related to the fusiform Reduced activation within the frontostriatal pathway

faces (Thomas et al., 2008) and emotions (Philippi et al., 2009). For example, Philippi et al. (2009) showed that focal lesions of the IFOF are associated with impaired recognition of emotional facial expressions. Combined, these studies indicate that white matter matures rapidly during early brain development and that the structural integrity of the IFOF is associated with face and emotion processing.

It is possible that altered development of the IFOF in WS may be a cause or a consequence for some of the distinctive patterns of face processing in this condition. For example, rapid or spared development of the IFOF may occur in contrast to relatively delayed or impaired development of dorsal stream pathways important for visuo-spatial functioning such as the SLF. DTI studies in adults with WS provide preliminary support for this hypothesis. For example, Marenco et al. (2007) demonstrated that adults with WS exhibit greater lattice index (LI: a measure of microscopic directional organization) of white matter fibers within the IFO (part of the IFOF), as compared to controls. Hoeft et al. (2007) demonstrated that altered structural integrity of the SLF is associated with visuo-spatial deficits in adults with WS. Lastly, in a recent study from our laboratory, we demonstrated that white matter fibers projecting through the fusiform gyrus (likely overlapping with fibers within the IFOF) were greater in volume, fractional anisotropy and density in WS relative to controls (Haas et al., 2012; **Figure 3**). Rapid or spared development of the IFOF and delayed or impaired development of the SLF may be a primary or secondary neural substrate associated with increased affinity to processing faces and delayed visual-spatial functioning in WS.

AMYGDALA NUCLEI

During typical development, the amygdala increases in volume between the ages of 4 and 18 years of age (Giedd et al., 1996; Durston et al., 2001). Functionally, younger children (3.5–8.5 years of age) exhibit greater amygdala response to happy, relative to angry faces, whereas adults exhibit greater amygdala response to angry, relative to happy faces (Todd et al., 2010). Nuclei within the amygdala are anatomically distinct and exhibit different (and interactive) functional roles (Aggleton, 2000; Balleine and Killcross, 2006). For example, the basolateral nucleus receives input from sensory cortices (Saygin et al., 2011) and some studies have suggested is primarily involved in the formation of stimulus-value associations during fear conditioning (LeDoux et al., 1990; Koo et al., 2004). Other amygdala nuclei have been shown to serve different functions. For example the central nucleus is thought to be preferentially involved in the moderation of appetitively motivated learning processes (Knapska et al., 2006; Mahler and Berridge, 2009; Lee et al., 2010). While the spatial resolution of fMRI substantially limits the ability to accurately differentiate structure-function associations of amygdala nuclei in humans (Ball et al., 2009), single-unit recording studies in primates have reported on the presence of specific emotion (e.g., aversive vs. pleasant) selective neurons within the amygdala (Paton et al., 2006; Belova et al., 2007). Overall, these studies indicate that the structure and function of the amygdala develops throughout childhood and there is evidence that amygdala nuclei are anatomically and functionally dissociable. In addition, there is some evidence that the basolateral nucleus may be particularly engaged during the processing of negative social stimuli (LeDoux et al., 1990; Koo et al., 2004) while other nuclei, such as the central nucleus, may be particularly engaged during the processing of positive social stimuli (Knapska et al., 2006; Mahler and Berridge, 2009; Lee et al., 2010).

In WS, the amygdala nuclei important for processing social-emotional signals may not develop normally and may either be a cause or a consequence of atypical patterns of emotion processing. In adults with WS, regions within the amygdala that exhibit altered reactivity to fearful and happy faces appear to have a different functional topography. For example, the results of an fMRI study from our laboratory indicated that the location of the amygdala cluster found to be more responsive to fearful faces in TD controls is relatively more inferior (peak MNI z coordinate $= -20$) compared to the location of the cluster found to be more responsive to happy faces in WS (peak MNI z coordinate $= -14$; Haas et al., 2009; **Figure 4**).

In may also be the case that WS is associated with delayed (as opposed to atypical) development of the amygdala. As with TD children (Todd et al., 2010), adults with WS exhibit greater amygdala reactivity to happy (relative to negative emotional) facial expressions (Haas et al., 2009). Thus, in WS the amygdala may be delayed in terms of developing a heightened sensitivity to negatively valenced (socially related) stimuli.

Another intriguing theory regarding amygdala development in WS involves the association between the amygdala and serotonin function. Specifically, differential development of amygdala nuclei in WS may, in part, be associated with the serotonin system. This hypothesis is supported by evidence that mouse models of WS exhibit altered serotonin metabolism within the amygdala (Young et al., 2008) and that the basolateral and central nuclei within the amygdala differ according to the amount of serotonergic innervation (Lehmann et al., 2003). Lastly, there is some evidence that serotonin transmission may be related to the social phenotype of WS (Reiss et al., 1985; Proulx et al., 2010). Taken together, atypical or delayed development of the amygdala, and

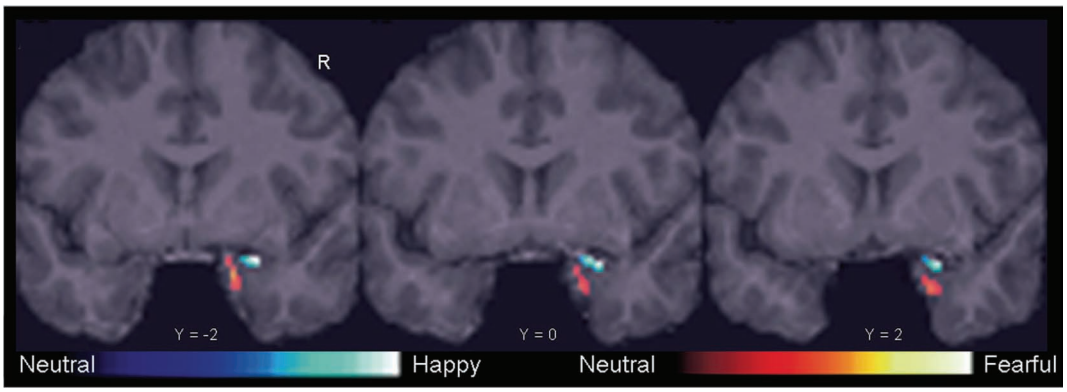

FIGURE 4 | Areas of greater right amygdala reactivity to fearful and happy facial expressions (compared to neutral) within the Williams syndrome (WS) and typically developing (TD) groups. Voxels of greater activation in response to happy versus neutral facial expressions in the WS group are designated by cold colors (blue). Voxels of greater activation in response to fearful versus neutral facial expressions in the TD group are designated by hot colors (orange). Adapted from Haas et al. (2009) Journal of Neuroscience.

serotonergic function within the amygdala, may be an important cause or consequence of distinctive patterns of emotion processing in WS.

DISTRIBUTED NETWORK

Throughout typical childhood development, the amount of information processed locally *decreases* while the amount of information processed throughout a distributed neural network *increases* (Uddin et al., 2010; Vogel et al., 2010). For example, Supekar et al. (2009) used a combined functional connectivity and DTI approach to show that childhood brain development is associated with a weakening of short-range and a strengthening of long-range connectivity. Interestingly, increased long-range connectivity (such as within the brain's default mode) is thought to be a neural construct associated with the development of complex, higher order social-cognitive abilities such as self-reflection and theory of mind (Uddin et al., 2007; Spreng et al., 2009).

Throughout typical development, many other changes occur in terms of how the cortex of the brain is structurally organized. For example, the complexity of cortical folding patterns (i.e., gyrification) peaks during early childhood and then decreases throughout late childhood, adolescence, and adulthood (Raznahan et al., 2011). Alterations of gyral and sulcal patterns are associated with cortical fiber connections (Takahashi et al., 2011) and thus are related to how neuronal signals are integrated throughout the brain (White et al., 2010). Models of cortical complexity suggest that many factors that include synaptic pruning, neuronal packing density, differential expansion of cellular layers and/or tissue types (gray vs. white matter) affect the emergence of cortical folding patterns throughout typical development (Van Essen, 1997; White et al., 2010; Mangin et al., 2011). In summary, during typical development, the connections within the brain, as well as the organization of the cortex, undergo many functional, and structural changes that likely correspond with the development of complex social-cognitive functions.

In WS, aberrant development of long- vs. short-range connectivity patterns may be a cause or a consequence of atypical abilities underlying the integration of social-cognitive stimuli. Individuals with WS exhibit spared (or even heightened) ability to process specific, simple types of social stimuli (i.e., features of faces; Karmiloff-Smith et al., 2004; Annaz et al., 2009; Isaac and Lincoln, 2011), but exhibit delays in integrating large sets of social-cognitive information (Tager-Flusberg and Sullivan, 2000; John and Mervis, 2010). In WS, the development of long-range connectivity patterns may be delayed with respect to short-range connectivity patterns. Aberrations of distributed long-range neural networks in WS may in part be associated with how the brain is globally organized. Indirect evidence for this hypothesis comes from findings showing that overall, the WS brain (in adulthood) is smaller in volume (∼12%; Reiss et al., 2004; Thompson et al., 2005), has a relatively lower proportion of white matter (Thompson et al., 2005) and has a more complex pattern of cortical folding (Schmitt et al., 2002; Kippenhan et al., 2005; Van Essen et al., 2006) relative to the TD brain. Interestingly, fMRI studies have reported preserved local activation paired with reduced functional connectivity when individuals with WS perform visual-spatial (Meyer-Lindenberg et al., 2004) and social-cognitive (Sarpal et al., 2008) tasks. Lastly, there is evidence that individuals with WS exhibit alterations in neuronal development. For example, post mortem studies (in humans) have shown that WS is associated with an increase in packing density of neurons (Galaburda and Bellugi, 2000) and animal models of WS exhibit alterations in synaptic plasticity and dendritic spine morphology (Osborne, 2010). In summary, alterations or delays in how distributed long-range networks develop in WS may be an important neural correlate of deficits in higher order social-cognitive functions in WS.

GENE X ENVIRONMENT INTERACTIONS

Although there is considerable support for a model relating genetic risk in WS to atypical brain development, ultimately influencing distinctive social behaviors in this condition, it is also important to consider the influence of environmental factors. Altered neural circuitry may also be a consequence of atypical social behavior and/or environmental factors operating throughout development in WS. It is well established that genes and environmental factors

interact with one another to influence many psychological traits (Dick, 2011). In addition, it is well recognized that the trajectory and severity of symptoms associated with many neurodevelopmental conditions are affected by environmental factors (Reiss and Dant, 2003; Zahir and Brown, 2011).

Though individuals with WS are at significant risk for demonstrating characteristic features of the behavioral phenotype discussed above, persons with this condition also exhibit considerable variability in cognitive ability and social functioning. In terms of cognitive abilities, Berman and colleagues have reported on an atypical group of individuals with WS that exhibit relatively normal IQ (Meyer-Lindenberg et al., 2005; Marenco et al., 2007; Sarpal et al., 2008), while the majority of individuals with WS exhibit IQ scores between 50 and 60 (Martens et al., 2008). The fact that there can be considerable variability across cognitive functions in WS suggests that other factors, such as those related to the environment and genes outside the critical WS deletion region on chromosome 7, may be at play.

In terms of social behavior, it is also clear that there exists considerable variation in how emotions and social stimuli are processed in WS. For example, Porter et al. (2008) demonstrated that individuals with WS exhibit significant heterogeneity across several measures related to theory of mind. In addition, we have described how individuals with WS exhibit variability in the tendency to approach strangers and that variation in social behavior is associated with amygdala response to fearful facial expressions (Haas et al., 2010; **Figure 2**). Although gene by environment interactions in WS has yet to be thoroughly investigated, this may be a promising avenue for future research.

TYPICAL SOCIAL BRAIN DEVELOPMENT AS INFORMED BY WS

By understanding the neural substrates of distinctive patterns of social behavior and emotion processing in WS, a greater understanding of how the typical social brain develops can be achieved. Additionally, because WS is linked to a specific and well defined contiguous genetic deletion, the study of individuals with this condition has the potential to provide important information pertaining to genetic factors that influence development of the typical social brain.

Recent studies on animal models of WS suggest that specific genes may be associated with the development of brain regions important for social behavior. For example, Feyder et al. (2010) utilized a histological approach in knockout mice and showed that *Cyln2* expression (a candidate gene for WS) and *DLG4* variation are associated with subtle dysmorphology of amygdala dendritic spines. These findings suggest that *Cyln2* and *DLG4* may interact with one another to influence the development of the social brain.

Other studies of humans with partial WS deletions also support the hypothesis that specific genes may influence the development of the social brain. Dai et al. (2009) compared the social behavior of an individual with a large portion of the WS affected genes deleted, but spared *GTF2I*, to a group with the full WS deletion. Results indicated that the individual with a spared *GTF2I* gene was less social as compared to the group with the full WS deletion. Together, these findings suggest that some of the WS affected genes (including *Cyln2* and *GTF2I*) may influence the typical development of the social brain.

FUTURE DIRECTIONS

In this article we have presented a framework of how the social brain may develop in WS by using an integrative approach. We have described how particular neural mechanisms may be associated with the development of atypical social behavior and emotion processing in this condition. Future research using prospective, longitudinal designs paired with advanced neuroimaging techniques and behavioral measurement approaches will be critical to further elucidating social brain development in typical development and in WS. Below, we describe specific research strategies that may further elucidate social brain development in WS.

A potential strategy to elucidate how the cortical representation of faces develops in WS is to measure the volume of the FFA in a longitudinal fashion throughout childhood and adolescent development in WS using a face processing task and high-resolution fMRI (Golarai et al., 2007, 2010b). Tasks involving the presentation of different types of visual stimuli (including faces, objects and houses) are effective tools to quantify the proportion of the fusiform gyrus specifically responsive to faces vs. other visual stimuli (Berman et al., 2010). This strategy allows for statistical comparisons to be made regarding brain regions specialized for face processing in spite of potential structural differences within the fusiform gyrus associated with diagnosis or age (Grill-Spector et al., 2008). In addition, by pairing functional neuroimaging with behavioral face processing tasks in a longitudinal study, insight as to increased FFA volume either serving as a cause or a consequence to increased attention to faces in WS may be obtained.

Studies designed to elucidate how connections within the ventral stream develop in WS may include measuring the integrity of major white matter pathways within the brain during development by using a combined DTI and functional connectivity approach (Ramnani et al., 2004). DTI is a particularly advantageous tool to measure condition specific alterations in white matter (Thomason and Thompson, 2011) and developmental changes in brain connectivity patterns (Johnston, 2008). Combining DTI with functional connectivity approaches is particularly useful to better understanding how white matter pathways contribute to processing information between critical brain regions (Guye et al., 2008). Using this approach may be useful in testing the hypothesis that the rate of development of pathways within the ventral stream, such as the IFOF, occurs differently as compared to dorsal pathways, such as the SLF, in WS.

A potential strategy to elucidate amygdala development in WS is to measure the anatomy and function of amygdala nuclei on a longitudinal basis during childhood and adolescence (Solano-Castiella et al., 2011). Additionally, the use of an approach designed to quantify surface contours of the amygdala (*in vivo*) may provide insight as to how amygdala regions differentially develop in WS (Kim et al., 2011). Lastly, we may gain insight as to the development of amygdala function in WS by using fMRI paired with tasks including both positive and negative social stimuli (Gao and Maurer, 2009).

Lastly, studies designed to investigate how distributed neural networks develop in WS may include resting state fMRI combined with DTI and advanced analysis strategies such as functional connectivity and graph theoretical analyses. It may also be advantageous to include the assessment of higher order social-

cognitive functions such as theory of mind throughout development. Such approaches can be useful in characterizing the development of short vs. long-range connections within the brain (Supekar et al., 2009; Power et al., 2010) and may be used to test hypotheses that posit associations between distributed neural networks and the development of higher order social-cognitive functions (Uddin et al., 2007; Spreng et al., 2009) in WS.

CLINICAL IMPLICATIONS

Teaching appropriate social behavior to children with WS is among the most frequent challenges that parents and caregivers of children with WS report (Eleanor and Rosner, 2003). Furthermore, there are many clinical examples of adults with WS exhibiting persistent distinctive social behaviors that ultimately hinders their ability to lead normal lives (Bedeschi et al., 2011). Research that elucidates how distinctive social behaviors develop in WS is a critical step toward the design of effective intervention techniques that serve to improve social developmental trajectories in WS.

Understanding social brain development in WS may facilitate the design of novel intervention techniques. By understanding the trajectory of brain development in WS, clinicians may be better informed as to the optimal time to intervene. For example, Annaz et al. (2009) demonstrated that between the ages of 5.6–12.1 years, children with WS exhibit an emerging specialization to process individual features of faces (featural-based face processing – i.e., eyes and mouth), rather than holistically (i.e., the whole face combined). Therefore, one might predict that the 5–12 year age range may be a particularly advantageous developmental stage for interventions designed to improve face processing in WS. The use of brain imaging at multiple time points during development may serve as an important tool to measure the efficacy of interventional approaches for altering the structure and function of specific neural circuits in WS as has been suggested for other neurodevelopmental conditions such as fragile X (Fung et al., 2012). Lastly, as with the WS behavioral phenotype, the neural signature of WS is characterized by both typical and atypical elements. By understanding the neural mechanisms that are typical in WS, clinicians may be better positioned to design intervention approaches that capitalize on relative strengths to improving relative deficits.

SUMMARY AND CONCLUSIONS

In this article, we have reviewed studies on the social phenotype of WS from childhood to adulthood. These studies demonstrate that WS is characterized by an affinity towards social interaction and that the trajectory of acquiring social-cognitive functions is either atypical or delayed in WS. Neuroimaging studies have demonstrated that during adulthood, WS is associated with many alterations within the neural circuitry important for social behavior and emotion processing. We used an integrative approach and described how the social brain may develop in WS. We also described how future research may further inform models of neural and behavioral developmental mechanisms in WS. In conclusion, there remain many intriguing questions regarding how the social brain develops in WS. We anticipate that research on social brain development in WS will further elucidate models of typical development of the social brain and will translate to improved developmental outcomes for affected individuals in the future.

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Social cognition in Williams syndrome: genotype/phenotype insights from partial deletion patients

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Identifying genotype/phenotype relations in human social cognition has been enhanced by the study of Williams syndrome (WS). Indeed, individuals with WS present with a particularly strong social drive, and researchers have sought to link deleted genes in the WS critical region (WSCR) of chromosome 7q11.23 to this unusual social profile. In this paper, we provide details of two case studies of children with partial genetic deletions in the WSCR: an 11-year-old female with a deletion of 24 of the 28 WS genes, and a 14-year-old male who presents with the opposite profile, i.e., the deletion of only four genes at the telomeric end of the WSCR. We tested these two children on a large battery of standardized and experimental social perception and social cognition tasks – both implicit and explicit – as well as standardized social questionnaires and general psychometric measures. Our findings reveal a partial WS socio-cognitive profile in the female, contrasted with a more autistic-like profile in the male. We discuss the implications of these findings for genotype/phenotype relations, as well as the advantages and limitations of animal models and of case study approaches.

Keywords: social cognition, Williams syndrome, partial deletion patients, genetic disorders, autism spectrum disorders, genotype/phenotype relations

INTRODUCTION

Williams syndrome (WS) has offered interesting insights into human social cognition in that, despite mild to moderately low IQ, individuals with WS present with an unusually strong social drive (Bellugi et al., 2000; Jones et al., 2000; Plesa Skwerer et al., 2011). A relatively rare neurodevelopmental disorder, WS is caused by haploinsufficiency for certain dosage-sensitive genes among the 28 genes in the WS critical region (WSCR) deleted from one copy of chromosome 7q11.23. WS can now be diagnosed at or shortly after birth, because the genetic basis – confirmed by a fluorescence *in situ* hybridization probe for the missing *ELASTIN* gene located at the center of the WS deletion – is usually suspected when cardiac problems in the form of supravalvular aortic stenosis and a typical WS facial dysmorphology are noted (Donnai and Karmiloff-Smith, 2000; Hammond et al., 2005). This means that current research not only can target older children and adults, but can also focus on infants and toddlers in the first 2 years of life (e.g., Paterson et al., 1999; Brown et al., 2003; Van Herwegen et al., 2008). This has allowed researchers frequently to note very early signs of the unusual social drive typical of the syndrome, in the form of infants' fascination with, and difficulty disengaging from, human faces.

The delineation of which of the 28 genes contribute to the unusual social phenotype is not straightforward, however, since 98% of children diagnosed with WS have the full WS deletion. Animal knock-out models have helped narrow the search for candidate genes (e.g., Osborne, 2010, 2012), but all animal models necessarily encounter the limitations that arise when researchers generalize to the neural, cognitive, and behavioral levels in humans. For example, although mouse chromosome 5G has the same 28 WSCR genes, albeit in reversed order, it cannot be simply assumed that across species the same genes have the same upstream and downstream regulatory pathways nor that they are expressed in homologous brain regions over developmental time. Moreover, single gene knock-outs do not replicate the WS 28-gene deletion, in that the targeted gene may interact in its expression with other genes in the deleted region. Additionally, it is critical to ensure that the tasks posed to mouse and human have the same cognitive-level demands, even if behaviorally they seem similar. Nonetheless, mouse models have been helpful in guiding human research in the socio-cognitive domain, although many open questions remain.

Another avenue of promise resides in the study of partial deletion (PD) patients who have smaller numbers of genes deleted in the WSCR, and who differ both from classical WS and from one another in terms of their socio-cognitive phenotypic profiles

(Frangiskakis et al., 1996; Botta et al., 1999; Tassabehji et al., 1999, 2005; Karmiloff-Smith et al., 2003; Gray et al., 2006; Smith et al., 2009). This paper focuses on two case studies, an 11-year-old female with 24 of the WS genes deleted except for four telomeric genes in the WSCR (up to *GTF2IRD1* although this gene is only partially deleted), leaving normal dizygosity of the four remaining telomeric genes, and a 14-year-old male with only those four telomeric genes deleted.

THE PARTIAL DELETION APPROACH

A number of individuals with PDs in the WSCR have been identified. Some of these patients have just two genes deleted – LIM domain kinase 1 (*LIMK1*) and ELASTIN (*ELN*) – while others have three, four, or five deleted (Frangiskakis et al., 1996; Botta et al., 1999; Tassabehji et al., 1999, 2005; Karmiloff-Smith et al., 2003; Gray et al., 2006; Smith et al., 2009; Antonell et al., 2010). These studies have mainly focused on the relationship between *ELN* and connective tissue defects, between *LIMK1* and spatial cognition, and between *GTF2IRD1* and craniofacial development in WS. However, with the identification of animal models that have highlighted the role of the *Gtf2ird1* gene as a general transcription factor affecting the expression of other genes (Young et al., 2008), PD patients with this gene either deleted or not deleted present interesting comparison cases. The animal model showed that mice with a heterozygous or homozygous disruption of *Gtf2ird1* exhibit decreased fear and aggression as well as increased social behaviors like excessive grooming of conspecifics, reminiscent of the WS hypersociability and diminished fear of strangers (Young et al., 2008). By contrast, the *Gtf2ird1* mice did not present with other core features of WS, such as increased anxiety and problems with spatial learning. The researchers also investigated possible neurochemical bases for the altered social behaviors in the mice and pinpointed increased levels of serotonin metabolites in several brain regions, including the amygdala, frontal cortex, and parietal cortex, which have previously been implicated in fear and aggression. Young et al.'s (2008) results suggest that hemizygosity for *GTF2IRD1* in humans may play a role in the complex behavioral phenotype seen in WS, either on its own or in combination with other genes, and that the *GTF* transcription factors at the telomeric end of the WSCR may have a general influence on social behavior through the alteration of neurochemical pathways.

Deletion of human *GTF2I* has also been implicated in intellectual difficulties associated with WS (Morris et al., 2003). Morris et al. (2003) assessed five families whose deletions spanned various sections of the WSCR, but with no deletions that included the centromeric *FKBP6* or the telomeric *GTFI* genes. Although all individuals presented with some aspects of the WS profile, none had the fully expressed WS phenotype and none had intellectual difficulties. Given the results of a case study that also found that deletion of *FKBP6* did not result in intellectual difficulties (Karmiloff-Smith et al., 2003), the findings of Morris et al. (2003) suggest that *GTF2I* deletions are the most likely candidates contributing to the intellectual deficits associated with WS (see Antonell et al., 2010 for full review).

Typical and atypical duplications and deletions of the WSCR have also been identified in some individuals presenting with a co-morbid autistic-like phenotype (Berg et al., 2007; Depienne et al., 2007; Malenfant et al., 2011), with *GTF2I* suggested to be the most likely candidate gene for the expression of autistic-like characteristics in these cases. Thus, although the complete deletion of the WSCR, including the telomeric *GTF2I*, is likely to result in the classic WS social phenotype, altered expression or duplication of *GTF2I* at the telomeric end of the WSCR may have disparate effects.

TWO HUMAN CASE STUDIES

Given the probable importance of the three *GTF2* transcription factors for the social phenotype of WS, we focused on two individual case studies, an 11-year-old female (HR in Tassabehji et al., 2005) with 24 genes deleted in the WSCR (up to GTF2IRD1) and a 14-year-old male (JB) with only the four telomeric genes deleted. **Figure 1** shows the typical WSCR together with the genetic deletions of these two patients (see also Antonell et al., 2010 for other examples of PDs). Psychometric testing and five experimental social perception and social cognition tasks were administered to each participant. In addition, the children's parents were asked to complete seven parent-rated standardized questionnaires, covering a range of social skills from Communication, Social Awareness, Social Cognition, and Daily Living Skills, as well as Anxiety.

MATERIALS AND METHODS

PARTICIPANTS

HR is a female, chronological age at testing: 11 years, 9 months. JB is a male, chronological age at testing: 14 years, 2 months.

MEASURES

Measures of cognitive functioning included the British Ability Scale-II School Age (BAS-II; Elliot et al., 1996), consisting of a number of tests designed to measure Verbal Ability, Non-Verbal Reasoning Ability, and Spatial Ability. The Raven's Coloured Progressive Matrices (RCPM; Raven et al., 2003) was administered as an additional test of non-verbal ability.

Theory of mind (ToM) and social cognition were assessed experimentally using the Social Attribution Task (Castelli et al., 2002), a measure of an individual's ability to attribute social meaning to animated geometric shapes, and The Strange Stories Task (social and non-social stories; White et al., 2009). We also used two explicit ToM tasks: the Smarties Task and the Where-will-she-look Task (Hogrefe et al., 1986), as well as an implicit ToM task which measures spontaneous anticipatory eye movements rather than

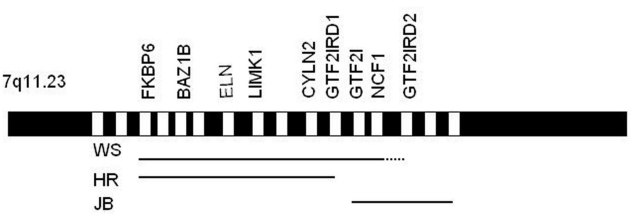

FIGURE 1 | Williams syndrome region. Lines represent the regions typically deleted in patients with WS, and the individual deletions of HR and JB. Only some of the main genes are shown. (Not drawn to scale).

verbal questioning (Senju et al., 2009). The seven standardized questionnaires included the Vineland-II (Sparrow et al., 2005), the Social Responsiveness Scale (SRS; Constantino and Gruber, 2005), the Sociability Questionnaire (Jones et al., 2000), the Children's Communication Checklist-2 (CCC-2; Bishop, 2003), the Children's Behavior Questionnaire (CBQ) – short form (Putman and Rothbart, 2006), the Spence Children's Anxiety Scale (SCAS; Spence, 1998), and the State-Trait Anxiety Inventory for Children (STAIC; Spielberger et al., 1973). Brief descriptions of the experimental tasks and questionnaires are given below.

EXPERIMENTAL TASKS

Social attribution task

Participants are shown four short animations which depict two triangles moving about on a computer screen in three different conditions: moving randomly, moving in a goal-directed fashion (chasing, fighting), and moving interactively with implied mental intentions (coaxing, tricking, wanting). In typically developing (TD) controls, the last condition frequently elicits descriptions in terms of mental states that participants attribute to the triangles in an anthropomorphic way. Participants are asked to watch each animation and give a verbal description of what is happening. Analyses are based on the differences between conditions in terms of the mental state descriptors produced.

Strange stories task

The participant reads (or if there is a reading difficulty, the experimenter reads) a series of short stories, some of which are mental state stories about human interactions/intentions and some physical stories about events. Each story is followed by a critical question (e.g., mental state: "why did he say this?"/"why will he look in the cupboard?"; physical state: "why were all the houses dry?"/"why did this happen?") and scored on the basis of mental attributions for social stories and causal inferences for non-social stories. Since the full task is very long, we selected five representative stories of each type of story, i.e., a total of 10.

Smarties task

Participants are shown a tube of Smarties (M&Ms), which the experimenter shakes to indicate that there is something inside. The parent then leaves the room. The child is asked to guess what is inside and always replies "Smarties." The experimenter then opens the tube to reveal its contents: paperclips. The child is then asked: "When your mummy returns, and I show her the closed tube, what will she say is inside?" and to justify their answer. The answer "Smarties" implies that the child understands that the parent's reply depends on what the parent *thinks* (that she holds a false belief), whereas the answer "paperclips" implies that the child does not have a first order ToM and simply replies on the basis of the state of the real world.

Where-will-she-look task?

This task is similar to the Smarties Task, but involves a box, a basket and a delicious biscuit. The experimenter puts the biscuit into the basket in front of the parent and child. The parent is then asked to leave the room. The experimenter then moves the biscuit from the basket and puts it into the box. The child is asked where the parent will look for the biscuit when she returns. The answer "in the basket" implies that the child understands that her parent holds a false belief about the biscuit's whereabouts, i.e., that the child has a first order ToM.

Implicit ToM task

Participants are shown a scenario on a computer screen very similar to the content of the above task, in which a little bear hides an object in one of two containers while a person on the screen is looking on. Then, when the human has her back turned, the bear moves the object into a different container. Eye tracking is used to measure exactly where the participant spontaneously looks in anticipation of which container the experimenter will reach toward as she turns back to retrieve the object.

QUESTIONNAIRES FILLED IN BY THE PARENTS

Vineland-II

The Vineland-II provides a measure of personal and social skills. An Adaptive Behavior Composite (ABC) Score is derived from standard scores in the Communication, Daily Living Skills, and Socialization domains. A separate scaled score for Maladaptive Behavior can also be obtained, which is a composite of Internalizing scores (avoids social interaction, overly anxious, cries/laughs too easily) and Externalizing scores (impulsive, temper tantrums, lies, cheats, steals, says embarrassing things).

Social responsiveness scale

The SRS is a measure of social reciprocal behavior. It provides a total *T*-score, which is a composite of five sub-scales: Social Awareness (ability to pick up on social cues), Social Cognition (ability to interpret social cues once picked up on), Social Communication (expressive social communicative abilities), Social Motivation (level of motivation to engage in social-interpersonal behaviors), and Autistic Mannerisms [stereotypical behaviors or highly restricted interests characteristic of autism spectrum disorders (ASD)].

Sociability questionnaire

The Sociability Questionnaire is a 16-item rating scale questionnaire, which includes items relating to social approach behavior and assessment of others' emotional states.

Children's communication checklist-2

The CCC-2 provides scores for 10 sub-scales as well as a General Communication Composite and Social Interaction Deviance Composite. It is particularly useful for examining language use (pragmatics) rather than language structure.

Children's behavior questionnaire

The CBQ Short Form is a 94-item assessment of temperament, which provides scores for 15 behavior sub-scales. The behavior scales which are social in nature include: Approach/Positive Anticipation, Anger/Frustration, Falling Reactivity/Soothability, Impulsivity, Inhibitory Control, Sadness, Shyness, Smiling and Laughter.

Spence children's anxiety scale

This consists of 38 items yielding a total anxiety score, also broken down into six sub-scores (panic attack and agoraphobia, separation anxiety, physic injury fear, social phobia, obsessive compulsive disorder, and general anxiety/overanxious disorder).

State-trait anxiety inventory for children

On the basis of 40 items, this provides a general measure of state anxiety and of trait anxiety in school-aged children.

RESULTS

EXPERIMENTAL TASKS

Social attribution task

On this task, HR's storytelling clearly differentiated between happenings suggesting mental states (e.g., "the big triangle wanted to get the little one to stay in his house"/"the little triangle was teasing the other one because she didn't want the big one to kiss her") and those involving physical events ("they're chasing each other"/"I don't know, they just seem to be moving around"). By contrast, JB's descriptions were similar for all types of event, and he failed to use mental state terms to describe any of the triangles' actions.

Social/non-social stories

On this task, HR's answers again clearly differentiated between events suggesting mental states ("it wasn't true, he didn't really like her hat, but he said that because he didn't want to hurt his aunt"/"he thought the policeman knew he'd stolen stuff from the shop") and the physical stories (e.g., "the little chicks lost their feathers because the big ones attacked them"/"maybe because the ground was shaking"). Again JB's responses failed to include mental state terms for the social stories nor to differentiate between social and non-social ones, although he was slightly more accurate than HR in inferring why some of the physical states occurred.

Smarties task

Both HR and JB responded correctly on this task.

Where-will-she-look Task?

HR clearly distinguished between where her mother thought the biscuit was and where it actually was, laughing as she responded, indicating that she knew her mother had been tricked and would respond incorrectly because of her false belief. By contrast, JB had difficulty with this task, changing his mind about where his father would look. We ran a second version of the task later in the testing session, but JB showed no signs that he understood the mental state implications of the task.

Implicit ToM task

Both HR's and JB's spontaneous anticipatory eye movements (i.e., first look) suggested that they had some implicit knowledge of the adult's false belief and of where the adult would first reach when she turned back to retrieve the ball.

PSYCHOMETRIC TESTING

The results of the psychometric testing are summarized in **Tables 1** and **2**.

British ability scales

HR's Verbal standard score was 80 (9th percentile). This was calculated from two core scales, Verbal Similarities (T-score = 44; 27th percentile, age equivalent = 10 years, 3 months) and Word Definitions (T-score = 31; 3rd percentile, age equivalent = 7 years, 7 months). In contrast, JB's Verbal standard score was only 59 (0.3 percentile). This was similarly calculated from two core scales, Verbal Similarities (T-score = 28; 1st percentile, age equivalent = 8 years, 3 months) and Word Definitions (T-score = 20; 1st percentile, age equivalent = 6 years, 7 months).

On Non-Verbal Reasoning, HR's standard score was 98 (45th percentile). This was calculated from two core scales, on both of which her performance was age-appropriate: Matrices (T-score = 52; 58th percentile, age equivalent = 12 years, 9 months) and Qualitative Reasoning (T-score = 46; 34th percentile, age equivalent = 11 years, 3 months). In contrast, JB showed impaired performance, with a Non-Verbal Reasoning standard score of only 65 (1st percentile). This was calculated again from two core scales, on both of which his performance was impaired: Matrices (T-score = 38; 12th percentile, age equivalent = 10 years, 3 months) and Qualitative Reasoning (T-score = 20; 1st percentile, age equivalent of 7 years, 1 month). On the Spatial cluster, HR's standard score was 73 (4th percentile), calculated from the core scales Recall of Designs (T-score = 29; 2nd percentile; age equivalent = 6 years, 1 month) and Pattern Construction (T-score = 41; 18th percentile, age equivalent = 9 years, 3 months). Of note here, HR's pattern construction T-score is below the 20th percentile, and her mean T-score of 61, meeting two of the four criteria for the WS cognitive profile (WSCP; Mervis et al., 2000). In contrast, JB's Spatial standard score was 47 (0.1 percentile), also calculated from the core scales Recall of Designs (T-score = 20, 1st percentile; age equivalent <5 years) and Pattern Construction (T-score = 20; 1st percentile, age equivalent = 5 years, 4 months). His profile did not meet the WSCP.

HR's General Conceptual Ability Score (combination of the three cluster scores) was 80 (9th percentile), with a relative strength in Non-Verbal Reasoning and a significant difference (0.05 level) between the Non-Verbal Reasoning cluster scores and the Spatial and Verbal scores. Conversely, JB's GCA score was only 44 (0.1 percentile).

Raven's coloured progressive matrices

On the RCPM, HR achieved a total score of 32, a chronologically age-appropriate level on this task. In contrast, JB's total score was only 18, with performance below an age-appropriate level and yielding an estimated mental age of 7 years.

QUESTIONNAIRES

Comparisons of HR and JB revealed both similarities and differences across different aspects of social ability as evaluated by their parents.

Children's communication checklist-2

Both children had poor communication results on this test. HR achieved a General Communication Composite (GCC) score of 36 (2nd percentile) and Social Interaction Deviance Composite (SIDC) score of −2. In combination with a GCC score below 55,

Table 1 | Psychometric tests.

	HR (age = 11.9)	JB (age = 14.2)	Comments
BAS-II			
Verbal	80 (9th centile)	59 (0.3 centile)	HR relative strength in non-verbal abilities
Non-verbal	98 (45th centile)	65 (1st centile)	
Spatial	73 (4th centile)	47 (0.1 centile)	
General Conceptual Ability	80 (9th centile)	44 (<1st centile)	
RCPM			
	32 (normal range: age equivalent = 11 years)	18 (below normal range: age equivalent = 7 years)	

BAS-II, British Ability Scales-II, standard scores are presented. RCPM, Raven's Coloured Progressive Matrices, raw scores are presented.

Table 2 | Social questionnaires.

	HR (age = 11;9)	JB (age = 14;2)	Comments
CCC-2			
GCC	36 (2nd percentile)	50 (8th percentile)	Only HR shows ASD profile for communication
SIDC	−2	6	
SRS			
Total score	75	68	Both moderate deficits
Social Awareness	80	52	HR = severe deficit (≥ 76T)
Social Cognition	79	63	HR = severe (≥ 76T), JB = moderate (≥ 59T)
Social Communication	75	61	Both moderate deficits
Social Motivation	58	73	JB = moderate deficit (≥ 59T)
Autistic Mannerism	67	78	JB = severe deficit (≥ 76T)
Sociability	Scores 6–7	Scores 1–3	JB < HR ability to assess others' emotional states
CBQ			
Smiling/Laughter	6.17	2.67	Contrasting profiles
Anger/Frustration	5.83	3-5	Contrasting profiles
Impulsivity	6.00	3-5	
Shyness	2.00	6.67	
VINELAND-II			
ABC	70 (2nd percentile)	73 (4th percentile)	Both have similar impairments throughout
Communication	74	71	Both elevated level, but from different composite scores
Daily Living	66	74	
Socialization	75	80	
Maladaptive Behavior	20	19	
SCAS			
T-score	58	16	Mean for clinically anxious group = 42.48, mean for non-clinical controls = 25.04
Sub-scales:			
Panic/agoraphobia	15	1	
Separation anxiety	8	4	
Physical injury fear	7	0	
Social phobia	11	1	
Obsessive/compulsive	9	5	
General anxiety	8	5	
STAIC			
State anxiety	27, *T*-score = 43	23, *T*-score = 35	Normative mean *T*-score = 50. Both are below the mean for state anxiety. HR is above mean on trait (98th percentile)
Trait anxiety	51, *T*-score = 71	32, *T*-score = 42	

Standard scores are presented for CCC-2, Vineland-II, and STAIC questionnaires, T-scores are presented for SRS and SCAS questionnaires for "Sociability" and "CBQ" questionnaires, ranges of raw scores and mean raw scores are presented, respectively.

a negative SIDC value on the CCC-2 indicates a communicative profile suggestive of an autistic spectrum disorder. However, this was only true of HR, as JB's questionnaire results yielded a GCC score of 50 (8th percentile) and a SIDC score of 6.

Social responsiveness scale

Composite *T*-scores on the SRS questionnaire painted a somewhat different picture. JB's score was 68, whereas HR achieved a score of 75 (a higher score indicates poorer social responsiveness). Sub-scale *T*-scores over 60 reflect impaired behavior, and both participants' scores fell just short of the severe range. However, it is important to note that these similar composite measures masked different patterns of deficit. For HR, difficulty was apparent for Social Awareness (*T*-score: 80), Social Cognition (*T*-score: 79), and Social Communication (*T*-score: 75). The Autistic Mannerisms score (*T*-score: 67) did yield some deficits, but these were relatively less pronounced, whilst Social Motivation (*T*-score: 58) was not impaired in her case. JB presented with the opposite profile, with the most pronounced deficits for Social Motivation (*T*-score: 73) and Autistic Mannerisms (*T*-score: 78), borderline impairments for Social Cognition (*T*-score: 63) and Social Communication (*T*-score: 61). He had no deficit in Social Awareness (*T*-score: 52).

Sociability questionnaire

Further differences between HR and JB were observed in the ratings given for the Sociability Questionnaire. Ratings ranging from 1 to 7 indicate the likelihood of engaging with others, approaching others, or the probability of commenting on other's emotions. Higher scores indicate higher likelihoods of the behavior occurring, with a score of 4 reflecting typical behavior. HR's questionnaire results yielded mainly 6s and 7s for both approach behaviors and judgments of emotions, indicative of exaggerated social behaviors seen also in WS. However, HR had scores in the normal range with respect to interactions that involved strangers/unfamiliar adults (approach scores of 4s and 5s were given). By contrast, JB scored mainly 1s, 2s, 3s, which indicates a poor ability to assess another's emotional states and impaired social approach behavior (although scores of 6 were given when approach behavior related to family members).

Vineland questionnaire

Both HR and JB had low ABC Scores; HR had an ABC Score of 70 (2nd percentile) and JB had an ABC Score of 73 (4th percentile). This questionnaire yielded broadly similar profiles for HR and JB across the three contributing domains. For the Communication domain HR scored 74 (4th percentile), while JB scored 71 (3rd percentile). Scores in the Daily Living Skills and Socialization domains were again similar; Daily Living Skills: HR scored 66 (1st percentile) and JB scored 74 (3rd percentile); Socialization: HR scored 75 (5th percentile) and JB scored 80 (9th percentile). Within the Communication domain, however, HR had a lower age equivalent for Receptive Communication (5 years, 6 months) than for Expressive Communication (6 years, 6 months) and Written Communication (7 years, 9 months), but for JB Receptive Communication was relatively high (9 years, 6 months) compared to Expressive Communication (7 years, 6 months) and Written Communication (7 years, 9 months).

The Vineland also provides a Maladaptive Behavior score. Both HR and JB were categorized as having an elevated level of maladaptive behaviors (HR: 20; JB: 19). However, in HR this was driven by her elevated internalizing (score: 19) and externalizing (score: 20) scores, whereas for JB the internalizing score (score: 21) fell in the clinically significant range, but his externalizing score (score: 16) was average.

Children's behavior questionnaire

Ratings between 1 and 7 are given, with 7 indicating a high level of behavior for that scale. The social scales from this questionnaire revealed relatively high scores for HR for Smiling and Laughter (6.17), Anger/Frustration (5.83), and Impulsivity (6.00), and particularly low scores for Shyness (2.00). By contrast, JB's scores mainly ranged between 3 and 5, with the exception of relatively low scores for Smiling and Laughter (2.67) alongside high Shyness (6.67) scores.

Spence children's anxiety scale

HR reached a total score of 58, above the normative mean of 42.48 for those considered clinically anxious. Her sub-scores on the scale were: panic and agoraphobia = 15; separation anxiety = 8; physical injury fears = 7; social phobia = 11; obsessive/compulsive = 9; and general anxiety/overanxious disorder = 8. By contrast, JB's total anxiety score was only 16, which is below the normative mean (25.04) for non-clinical controls. His sub-scores were: panic and agoraphobia = 1; separation anxiety = 4; physical injury fears = 0; social phobia = 1; obsessive/compulsive = 5; and general anxiety/overanxious disorder = 5.

State-trait anxiety inventory for children

For state anxiety, HR had a raw score of 27 (*T*-score = 43), and JB had a raw score of 23 (*T*-score = 35). These scores are both below the normative mean of 50 for state anxiety. As far as trait anxiety is concerned, HR had a raw score of 51 (*T*-score = 71), which was well above the normative mean (98th percentile), whereas JB had a raw score of 32 (*T*-score = 42).

DISCUSSION

In summary, at the cognitive level, as measured on the BAS-II, JB presents with more profound impairments than HR, with scores on all his subtests at or below the 1st percentile. The pattern of his subscore tests is unlike that identified as the typical WSCP (Mervis et al., 2000), which at first blush could be expected given the sparing of most of the WS genes. However, other PD patients who do have many WS genes deleted but not the final four to six telomeric genes present with none of the WS phenotype except supravalvular aortic stenosis. Moreover, several groups now believe that the four telomeric genes in the WSCR are those which contribute most significantly to the WSCP. Thus, it could be considered surprising that JB fails to meet the WSCP because he has those four telomeric genes deleted. By contrast, HR's cognitive profile looks more like the WSCP, including a pattern construction score below the 20th percentile and below the mean *T*-score. Non-Verbal Reasoning assessed with the RCPM yields an age-appropriate score for HR, but an estimated mental age of only 7 for JB. From the results of the social questionnaires, both participants have moderate deficits.

However, on some sub-scales, they present with differing profiles. Of particular note, JB was found to have much more pronounced autistic mannerisms and very reduced social motivation compared to HR. Had the two children been more similar, one might have interpreted these differences in terms of gender. Although the role of gender may be implicated in gene–gene interactions that might account for some of the differences in the two profiles, HR's strong social motivation and JB's severe autistic mannerisms suggest that the dissimilarities between them cannot be due to this factor alone. Indeed, JB's initial diagnosis was ASD but subsequent genetic tests linked him to WS. JB also demonstrated greater impairments in assessing the emotional and mental states of others. On the CBQ, JB had higher levels of shyness, with a lower reported level of smiling/laughter. HR, in contrast, demonstrated high levels of smiling/laughter and low shyness. Nonetheless, it is important to note that the different standardized tasks sometimes varied in their results for the same individual with, for instance, some of HR's some results leaning to autistic-like traits and others to social disinhibition. Similar variations were found in JB's results. Our study therefore highlights the fact that findings from a single standardized task in group studies should be treated with caution, underlining the importance of deriving a general profile from several measures, particularly when using case studies.

The differing patterns were also evident in the results of the experimental ToM and social cognition tasks, with JB revealing considerably more deficits. However, surprisingly, he did succeed on the implicit ToM task, which is the opposite of the pattern typically witnessed in high-functioning individuals with ASD (Senju et al., 2009). It is worth noting that his success on the Smarties Task but failure on the Where-will-she-look Task may be explained by the fact that, although the Smarties Task is supposed to tap ToM attributions, participants can also give the right answer "Smarties" by using long-term semantic knowledge (i.e., Smarties tubes always contain Smarties), if the participant fails to use episodic knowledge of the current social scenario. In other words, although both children passed the Smarties Task, they may have done so by using different cognitive strategies. This, therefore, makes it unsurprising that JB failed on the Where-will-she-look Task, which cannot be solved on the basis of long-term semantic knowledge, but does not explain his success on the implicit ToM task.

One of the advantages (and, of course, limitations) of group studies is that they camouflage individual differences, which are often treated simply as noise. Although case studies allow for a richer database, they obviously suffer from the influence of individual differences in home and school environments, gender and age differences, changing gene expression, and many other individual differences all of which contribute in combined and complex ways to the phenotypic outcome. Nonetheless, we believe that case studies can further our understanding of genotype/phenotype relations as they pertain to social cognition. The important question in the current case study is whether the genetic and socio-cognitive similarities and differences between HR and JB help us to hone in on genotype/phenotype relations in the social domain.

Although several animal studies have suggested that when one copy of *GTF2IRD1* and *GTF2I* is deleted, they play a crucial role in social cognition and anxiety in WS, our case study comparisons suggest that they cannot do so alone. HR does not have both these genes fully deleted and yet she presents with many of the characteristics typical of the social phenotype of full-blown WS. Nonetheless, she clearly does not fit the profile in its entirety given her stronger non-verbal compared to linguistic abilities. Moreover, although her parents report that HR talks readily to strangers and is overly friendly, the team of researchers at the lab, who have tested HR repeatedly since she was 28 months of age, have all consistently judged that HR is currently considerably less uninhibited than their other WS participants. By contrast, while JB has these genes deleted, he presents with almost the opposite profile, with numerous autistic-like traits and none of the signs of social disinhibition characteristic of WS. The same holds for social anxiety, with HR scoring very highly and JB completely in the normal range. Hemizygosity for *GTF2I* has been implicated in elevated levels of sociability typical of WS (Dai et al., 2009). However, the current findings suggest that deletion of the telomeric genes alone, inclusive of *GTF2I* but without the remaining deleted genes on the entire WSCR, are insufficient to result in this phenotypic outcome.

Moreover, whereas HR has a slight WS facial morphology, JB has none of the facial traits typical of WS. So, although human genetic mapping data have implicated two related genes (*GTF2IRD1* and *GTF2I*) in the cause of some of the key features of WS, including craniofacial dysmorphology, hypersociability, social anxiety, and visuospatial deficits, this case study comparison suggests that, whatever their role, their contribution is likely to be in interaction with other genes proximal of the four telomeric genes in the WS critical region.

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Attention deficits predict phenotypic outcomes in syndrome-specific and domain-specific ways

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Attentional difficulties, both at home and in the classroom, are reported across a number of neurodevelopmental disorders. However, exactly how attention influences early socio-cognitive learning remains unclear. We addressed this question both concurrently and longitudinally in a cross-syndrome design, with respect to the communicative domain of vocabulary and to the cognitive domain of early literacy, and then extended the analysis to social behavior. Participants were young children (aged 4–9 years at Time 1) with either Williams syndrome (WS, $N = 26$) or Down syndrome (DS, $N = 26$) and typically developing controls ($N = 103$). Children with WS displayed significantly greater attentional deficits (as indexed by teacher report of behavior typical of attention deficit hyperactivity disorder (ADHD) than children with DS, but both groups had greater attentional problems than the controls. Despite their attention differences, children with DS and those with WS were equivalent in their cognitive abilities of reading single words, both at Time 1 and 12 months later, at Time 2, although they differed in their early communicative abilities in terms of vocabulary. Greater ADHD-like behaviors predicted poorer subsequent literacy for children with DS, but not for children with WS, pointing to syndrome-specific attentional constraints on specific aspects of early development. Overall, our findings highlight the need to investigate more precisely whether and, if so, how, syndrome-specific profiles of behavioral difficulties constrain learning and socio-cognitive outcomes across different domains.

Keywords: attention, literacy and early reading development, longitudinal data analysis, Down syndrome, Williams syndrome, neurodevelopmental disorders

INTRODUCTION

The ability to concentrate and stay focused on a task, to switch attention between tasks, and to inhibit impulsive responding are critical skills for early socio-cognitive learning and subsequent academic outcomes (Smallwood et al., 2007). The development of these attentional skills begins early in life, becoming progressively more robust from the preschool years onward (Gupta et al., 2009; Shing et al., 2010; Zhan et al., 2011). In the classroom, inattentive behavior in preschool children, but not hyperactive behavior, predicts poor reading outcomes in Grade 1 and also Grade 5 (Dally, 2006). Findings from a recent 16 year longitudinal study also indicate that inattention rather than hyperactivity during primary school significantly predicts long-term educational attainment and vocational choices (Pingault et al., 2011). Subtle distinctions across dimensions of attention in predicting later outcomes also emerge at the cognitive level: while executive processes relate concurrently and longitudinally to functioning across domains like literacy and numeracy (Bull et al., 2008; Welsh et al., 2010; Steele et al., in press). Furthermore, selective and sustained attention emerge as longitudinal predictors of numeracy but not literacy (Steele et al., in press). Accordingly, disruption to these essential processes can lead to increased levels of distractibility, impulsivity, forgetfulness, and poor focus. In the case of children who are especially vulnerable to attention impairments because of an underlying genetic neurodevelopmental disorder (e.g., Down Syndrome), attentional constraints will likely exacerbate an already compromised computational system. These in turn may reduce learning capacity and increase risk of academic failure, poor social relationships and long-term behavioral, and emotional problems.

Given the pivotal role of attention in typically developing children in driving early developmental changes and outcomes, but also more generally in shaping the broader socio-cognitive landscape, there is a pressing need to extend this research to atypical populations. Focusing on neurodevelopmental disorders with a clearly defined genetic origin, and pitting one against the other, provides a unique opportunity to explore how attention and other behavioral difficulties may differentially constrain learning and socio-cognitive outcomes across disorders and across developmental time.

In the current study, we focus on two neurodevelopmental disorders that have generated considerable research intensity: Williams syndrome (WS) which results from a heterozygous deletion of approximately 28 genes on chromosome 7 (Donnai and Karmiloff-Smith, 2000; Morris, 2010), and Down syndrome (DS) from a trisomy on chromosome 21 (Antonarakis et al., 2004). Both disorders have a well-documented profile of inattentive behaviors

that are life-long (see Cornish and Wilding, 2010; Scerif and Steele, 2011 for reviews); both are at increased risk for attention-deficit hyperactivity disorder (ADHD), sharing many of the behavioral symptoms associated with ADHD (Ekstein et al., 2011; Leyfer et al., 2006; Rhodes et al., 2010). For example, Leyfer et al. in one of the largest samples to date of children with WS ($n = 119$) reported that almost 65% had received a diagnosis of ADHD. Furthermore, both individuals with DS and WS suffer from significant and pervasive executive functioning deficits that may impact everyday attention experiences in real-world settings such as the classroom (Munir et al., 2000; Porter et al., 2007;Rhodes et al., 2011a,b). In particular, Rhodes et al. (2011b) found comparable levels of behavioral inattention symptoms coupled with working memory deficits in their WS and ADHD samples suggesting common developmental pathways and outcomes in early learning environments. Notably, both groups have early reading difficulties (Howlin et al., 1998; Bird et al., 2000; Laing et al., 2001; Byrne et al., 2002; Laws and Gunn, 2004).

Despite the identification of these cross-syndrome similarities, there are a number of core limitations in the current literature: (1) Although rich and informative, studies to date have rarely taken into account the role of development in shaping early phenotypic outcomes, and fewer still have investigated how the genetic constraints of a given disorder may interact with attention and other behavioral difficulties to impact socio-cognitive outcomes across developmental time points; and (2) In the case of spoken and written language acquisition which has strong links to attention, studies have yet to determine whether, irrespective of genetic origin, attention plays a similar predictive role concurrently and longitudinally for the communicative domain of vocabulary development and the cognitive domain of reading, as is the case for typically developing children. Alternatively, each neurodevelopmental disorder may have individual signatures in which attention or other behavioral problems predict trajectories that are syndrome-specific. Accruing this new knowledge is especially pertinent in light of recent findings that children with WS and DS differ uniquely from each other and from typically developing children in how they develop early reading skills (Steele et al., under review). To our knowledge, no study has assessed how, and if, attentional deficits alongside broader behavioral problems serve to constrain emerging vocabulary and reading levels in children with WS and DS. Such findings will form a much needed platform to develop targeted and developmentally appropriate syndrome-specific interventions across the early school years that can tap core behavioral weaknesses that underpin later socio-cognitive outcomes in children with neurodevelopmental disorders.

This study therefore had three principal aims. The first was to investigate early cross-syndrome differences in inattention, hyperactivity and other problem behaviors. We predicted that ADHD-like attention profiles would characterize both disorders differentiating them from typically developing children, but also that syndrome-specific profiles would emerge, that they would relate differentially to broader aspects of socio-behavioral strengths or weaknesses, and that they would change developmentally from Time 1 to Time 2. The second aim was to investigate whether vocabulary and reading development differed across disorders. We predicted that children with DS would be weaker compared to those with WS given their known socio-cognitive profiles (Bird et al., 2000; Byrne et al., 2002; Laws and Gunn, 2004), but that both groups would undergo developmental change from Time 1 to Time 2. Thirdly, through our prospective longitudinal design, we aimed to investigate whether attentional or behavioral profiles were predictors of vocabulary and single word reading concurrently as well as longitudinally 12 months later.

MATERIALS AND METHODS

PARTICIPANTS

Twenty-six children with DS were recruited through local DS support groups including the Downs Heart Group, South Bucks DS Group, and the Swindon Downs Group. The 26 children with WS were recruited through the WS Foundation. These charities sent information sheets and consent forms to all children on their databases between 4 and 8 years (see **Table 1**).

One hundred and three typically developing children ("TD children"), aged 3–7 years and evenly distributed across age groups and genders, also took part in the study. These children constituted a representative normative sample, as suggested by non-verbal ability scores on average of 49.95 (SD = 9.66, measured by the Pattern Construction-Subscale, BAS-II, t-scores with a population mean of 50) and verbal abilities on average of 104.77 (SD = 11.89, measured with the British Picture Vocabulary Scale-II, z-scores with a population mean of 100). TD Children were recruited from four local state primary schools and three local nurseries. Recruitment followed procedures set by the relevant research ethics review board whereby, following provisional interest in taking part in the study, information letters with consent slips were sent home to parents. None of the TD children had a diagnosed learning disability or reported clinically diagnosed attention disorder. In order to gage the degree of delay experienced by children with

Table 1 | Group demographics.

	DS ($N = 26$)	WS ($N = 26$)	NVMA controls ($N = 22$)	CA controls ($N = 81$)	Bonferroni corrected comparisons
Chronological age (months)	83.5 (14.1)	78.5 (11.3)	40.6 (3.3)	72.1 (13.5)	NVMA < CA = WS = DS
Non-verbal mental age (months)	38.3 (8.4)	38.2 (6.7)	43.1 (9.3)	72.7 (19.6)	DS = WS = NVMA < CA

Chronological and non-verbal mental age (means, standard deviations) for children with DS, WS, as well as a large sample of typically developing children ("CA") of equivalent chronological age, and a smaller group of non-verbal mental age controls ("NVMA") at Time 1. Because of violations of parametric statistics, where necessary non-parametric statistics and corrections for multiple comparisons were also employed.

DS or WS compared to their chronological age or level of ability respectively, TD children constituted two groups, one matched to the two syndrome groups on chronological age, "CA controls," and the second matched to them in terms of their non-verbal mental age ("NVMA controls"). Although it is frequent to match verbal mental age difficulties in studies including individuals with DS or WS, here we were aiming to examine literacy and early receptive language in their own right, and therefore aimed to control for group differences outside these target areas.

PROCEDURE

The schools provided a quiet area in which to complete the battery of tests at both time points. Task presentation was counterbalanced across TD, DS, and WS children.

MEASURES

Inattention/Hyperactivity profiles were measures as predictors at Time 1, whereas indices of developing vocabulary levels and literacy were measured at both Time 1 and Time 2, 12 months later.

Behavioral inattention/hyperactivity

As one of the measures of social problems, the Conners Teacher Rating Scale (Conners, 1997, "CTRS" henceforth) was chosen as it is a commonly used standardized screening instrument that targets ADHD symptomatology in the classroom. It consists of 28 items, measuring indices of oppositional behavior problems, hyperactive behavior, and cognitive/inattention problems across the school setting in 3–17 year olds. Three subscales address Oppositional behavior (e.g., refusal to comply with adults' requests, argumentative, spiteful), Cognitive Inattention (e.g., easily distracted, failure to finish tasks, forgetful, short attention span), Hyperactivity (e.g., restless, cannot remain seated at school, cannot wait for turn, excitable and impulsive), and an ADHD Index provides a composite score based on key items across the other three subscales (scores above the clinical cut-off level of 70 are considered likely to have ADHD, and scores above 65 are considered "at risk").

Socio-behavioral strengths and weaknesses

A second measure of social problems was derived from the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). Subscale scores for conduct, peer and emotional problems, hyperactivity, and prosocial behaviors are available (max 10 points each). They can also be summed into a total difficulties scale (max 40 points). Total difficulties scores above 15 are considered "abnormal," and so are subscales scores above three (Conduct), four (Peer problems), five (Emotional symptoms), six (Hyperactivity) or below five (Prosocial behaviors).

Non-verbal ability

Pattern Construction Subscale of the British Ability Scales-II (PC-Subscale, BAS-II; Elliott et al., 1996), which assesses visuo-spatial ability.

Receptive vocabulary

British Picture Vocabulary Scale-II (BPVS-II; Dunn et al., 1997).

Letter knowledge

Assessed following the Phonological Abilities Test protocol (PAT; Muter et al., 2004).

Phonological awareness

A phoneme matching task designed for pre-schoolers (Carroll and Snowling, 2001) assessed basic phonological awareness (PA), in which children are shown a familiar picture and told the name associated with it. They are then shown and told the names of two further pictures and asked which started with the same sound as the original picture. Words were one syllable Consonant-Vowel-Consonant words, known to the majority of 3-year-old children. Sixteen trials were presented. Rhyme awareness was assessed using a task identical to the phoneme task, except that children had to pick which of two named pictures rhymed with the target one. For both tasks, children were allocated a raw score as well as a score of 1 (signifying passing the task) if they obtained 12 or more items correct (above chance, binomial test), or a score of 0 if they made fewer than 12 correct responses.

Reading

Early Word Reading ability scale (EWR, Hatcher et al., 1994). This targets the earliest stages of word reading. Scores are based on the total out of 42 words read aloud correctly. Children scoring 34 or above were also asked to complete the single word reading subscale of the British Ability Scale-II (BAS-II, Elliott et al., 1996). As no standardized single word reading test exists for the full ability range of readers between 3 and 8, a combined "Single Word Reading" score was computed as follows: if a child completed only the EWR scale, their Single Word Reading score was the number of correctly read words on this measure. If they also completed the BAS-II reading subscale, their raw scores from both tests were added and 20 points were subtracted from this total to allow for the overlap in reading level across the EWR and the first 20 items of the BAS-II subscale.

DESIGN

At Time 1, inattention/hyperactivity, receptive vocabulary and early literacy profiles were analyzed by comparing scores on each dependent measure through ANOVAs, with Group as the between-subject factor. Concurrent relationships across measures for children with DS or WS were investigated through correlations. Longitudinal data at Time 2 were used to assess, first, changes in inattention and hyperactivity, vocabulary, and reading. Second, we assessed the predictive role of Time 1 inattention/behavioral scores for Time 2 vocabulary, single word reading, and multiple additional literacy measures for children with WS and DS. Hierarchical regression models followed statistically significant preliminary correlations, with attentional scores at Time 1 entered as predictors of Time 2 outcomes, together with their interaction with Group, to assess the extent to which group membership predicted Time 2 outcome differentially in combination with Time 1 predictor variables. It is the statistically significant interaction terms that we focus on as predictors, as they add to the basic correlations an assessment of syndrome-specific trajectories.

RESULTS

PROFILES AT TIME 1 AND CONCURRENT RELATIONSHIPS ACROSS DOMAINS

Behavioral inattention/hyperactivity profiles

Mean *t*-scores (standard error) for the CTRS are presented in **Table 2**. Children with WS had higher *t*-scores than both

Table 2 | Inattention and hyperactivity across groups.

	DS ($N = 23$)	WS ($N = 25$)	NVMA controls ($N = 22$)	CA controls ($N = 81$)	Statistics for the main effect of Group	Bonferroni corrected comparisons
Oppositional	66.7 (10.5)	68.3 (16.7)	56.1 (13.8)	53.7 (13.4)	$F(3,147) = 10.657$*	NVMA = CA < WS CA < DS
Cognitive problems/inattention	72.7 (9.4)	69.0 (12.3)	54.8 (10.9)	53.5 (12.6)	$F(3,147) = 22.640$*	NVMA = CA < WS = DS
Hyperactivity	59.5 (11.1)	65.7 (12.9)	54.7 (9.7)	51.0 (10.4)	$F(3,147) = 12.950$*	NVMA = CA < WS CA < DS
ADHD index	61.6 (12.3)	71.3 (12.5)	56.9 (9.7)	51.2 (10.9)	$F(3,147) = 21.885$*	NVMA = DS < WS CA < DS

*Mean (standard deviations) t-scores for the four subscales of Conners Teacher Rating Scale ("CTRS") for children with DS, WS, NVMA, and CA controls *p < 0.001.*

NVMA and CA controls on all subscales of the CTRS (highest $p = 0.016$, all comparisons Bonferroni corrected or analyzed non-parametrically where necessary). In contrast, children with DS had higher inattention than both CA and NVMA controls ($p < 0.001$ for both comparisons), but they did not differ significantly from NVMA controls in terms of oppositional, hyperactive behaviors, and ADHD Index (all $p > 0.05$), although on these measures they scored more highly than CA controls ($p < 0.008$). Children with WS had significantly higher ADHD symptomatology (ADHD Index) than children with DS ($p = 0.02$). In addition, 19 children with WS within our sample scored at or above 65 on the ADHD Index, the clinical cut-off for high risk of ADHD. This contrasts with only eight children scoring above cut-off amongst children with DS.

Vocabulary and literacy profiles

Table 3 presents scores for receptive vocabulary, single word reading, letter knowledge, rhyme, and phoneme matching tasks at Time 1. Children with WS had lower receptive vocabulary raw scores than CA controls ($p < 0.001$), but marginally higher scores than NVMA controls ($p = 0.06$), and significantly higher scores than children with DS ($p < 0.001$). Children with DS did not differ from NVMA controls ($p > 0.05$), comprehending fewer words than both CA controls and children with WS ($p < 0.001$). In terms of single word reading, both children with WS and those with DS read more words than NVMA controls, but fewer words than CA controls ($p < 0.001$). Both syndrome groups produced more letters than NVMA controls ($p < 0.001$) and did not differ from CA controls ($p > 0.05$). Rhyme matching for children with DS was equivalent to NVMA controls ($p > 0.05$) but poorer than that of children with WS ($p < 0.003$), who in turn were poorer on this ability than CA controls ($p < 0.001$). For phoneme matching, the pattern for children with DS was similar to rhymes, whereas children with WS performed at the level of CA controls ($p > 0.05$).

Socio-behavioral profiles

Figure 1 represents SDQ scores for children with DS or WS only, across all subscales (Emotional problems, Conduct, Hyperactivity, Peer problems, Prosocial behaviors) and Total difficulties. Children with WS had greater difficulties with Conduct ($p = 0.05$), Hyperactivity ($p = 0.026$), and Peer problems ($p = 0.022$) than children with DS, and this was reflected in a significantly greater number of reported Total difficulties ($p = 0.002$).

Concurrent relationships across domains

Table 4 reports correlation coefficients for the relationships between behavioral inattention/hyperactivity (CTRS *t*-scores) and all measures related to vocabulary, literacy and socio-behavioral strengths, and weaknesses for the two groups of atypically developing children. At Time 1, for children with WS there were no significant correlations between attention in the classroom, as gaged by teachers, vocabulary, and early literacy measures. In contrast, for children with DS greater behavioral deficits were in general negatively related to vocabulary and literacy indices: inattention related to smaller lexicon, single word reading scores, letter knowledge, and rhyme matching. Greater hyperactivity and ADHD index scores related to poorer letter knowledge and greater oppositional behavior to poorer phoneme matching.

In terms of socio-behavioral strengths and weaknesses, for children with WS oppositional behaviors on CTRS were positively correlated with conduct problems on SDQ. Greater inattention on CTRS correlated with greater conduct problems and hyperactivity as reported through SDQ. Furthermore, hyperactivity and ADHD Index on CTRS correlated with greater conduct problems, hyperactivity, and peer problems on SDQ. Poorer scores on all attention subscales of CTRS correlated with greater Total difficulties on SDQ. For children with DS, there were fewer statistically significant relationships overall between attention measures on CTRS and strengths and difficulties on SDQ. Greater oppositional behaviors related to greater conduct problems and hyperactivity. Greater inattention correlated with fewer prosocial behaviors. Hyperactivity and ADHD Index on the CTRS correlated with hyperactivity on SDQ. Only oppositional behavior on CTRS correlated with greater Total difficulties for this group.

LONGITUDINAL BEHAVIORAL PREDICTORS OF EMERGING VOCABULARY AND LITERACY ACROSS SYNDROMES

Longitudinal trajectories of vocabulary and literacy

Table 5 represents means, standard deviation, basic statistics for main effects of Time and Group for vocabulary and literacy measures at Time 1 and Time 2, for children with DS and children with WS. Overall, children with DS

Table 3 | Language and literacy profiles.

	DS ($N = 26$)	WS ($N = 26$)	NVMA controls ($N = 22$)	CA controls ($N = 81$)	Statistics for the main effect of Group	Bonferroni corrected comparisons
Receptive vocabulary	30.84 (11.64)	50.81 (58.58)	39.14 (10.81)	65.26 (16.65)	$F(3,151) = 39.563$*	DS = NVMA < WS < CA
Single word reading	11.3 (16.4)	9.3 (16.4)	0 (0)	31.68 (3.22)	$F(3,151) = 15.503$*	NVMA < DS = WS < CA
Letter knowledge	16.36 (8.90)	15.96 (8.74)	3.05 (7.61)	20.54 (0.91)	$F(3,151) = 25.615$*	NVMA < DS = WS = CA
Rhyme matching (% pass)	9.12 (2.71) (16%)	12.00 (3.68) (56%)	9.95 (3.27) (27%)	14.78 (0.28) (88%)	$F(3,151) = 33.878$*	DS: = NVMA; DS < WS < CA; WS = NVMA
Phoneme matching (% pass)	9.52 (3.02) (16%)	12.41 (9.52) (63%)	9.23 (2.49) (22%)	14.16 (0.35) (78%)	$F(3,151) = 23.129$*	DS = NVMA < WS = CA

Mean raw scores (SD) for language and literacy at Time 1. Where necessary, non-parametric statistics and corrections for multiple comparisons were also employed
*$p < 0.001$.

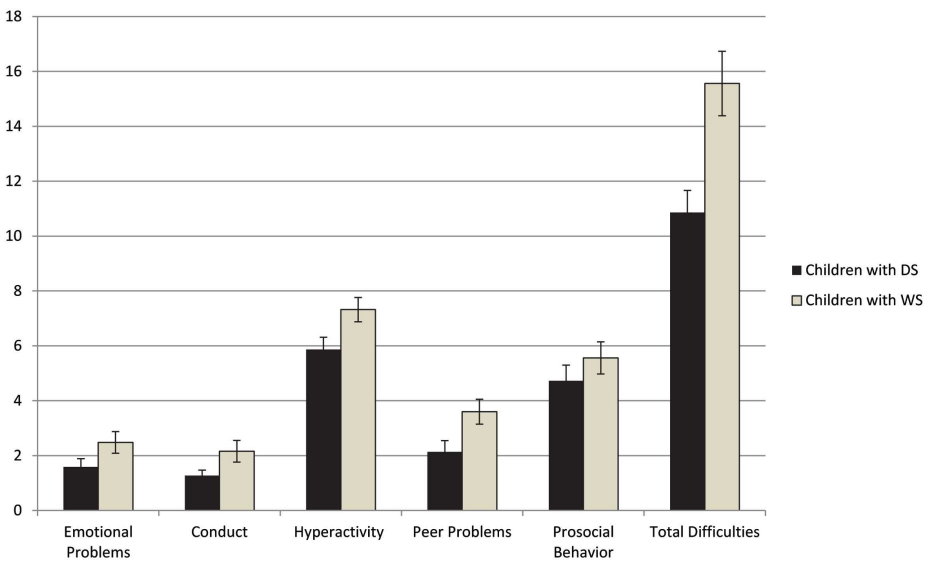

FIGURE 1 | Socio-behavioral strengths and weaknesses across syndromes. Note. Subscale raw scores and Total difficulties on SDQ for children with DS or WS.

and WS improved significantly on vocabulary and literacy, as indexed by significant main effects of Time for all measures except for phoneme matching. Furthermore, children with WS scored significantly higher than children with DS in terms of receptive vocabulary, rhyme matching, and phoneme matching, but the two groups did not differ for single word reading and letter knowledge. These differences and similarities remained stable over time, with no statistically significant interaction between Group and Time, highest $F(1,49) = 0.325$, $p = 0.571$.

Behavioral predictors of emerging vocabulary and literacy

Longitudinal (Time 1 to Time 2) Pearson's correlations between attentional measures (t-scores) at Time 1, receptive vocabulary and early literacy at Time 2 for children with DS and WS are reported in **Table 6**. Non-parametric Spearman's correlations were also employed to deal with violations of parametric statistics, and, unless otherwise stated, were consistent with their parametric equivalent. Overall, for children with DS greater behavioral deficits at Time 1 related to poorer vocabulary and literacy indices. Significant negative correlations were obtained for inattention and hyperactivity (all variables except for Time 2 single word reading). Known precursors of later reading (vocabulary, letter knowledge, rhyme, and phoneme awareness) related to CTRS scores for this group. We investigated the longitudinal relationships between T1 CTRS scores and T2 vocabulary/literacy outcomes further by testing whether they reached significance having controlled for baseline individual differences in T1 vocabulary/literacy. This approach allows testing whether attention measures predict change in vocabulary/literacy measures over and above early differences in these. A number of longitudinal relationships survived this further analysis (see **Table 6**) for children with DS. In contrast, for children with WS earlier behavioral deficits did not relate

Table 4 | Pearson correlations at Time 1.

	T1 Oppositional	T1 Cognitive problems/inattentive	T1 Hyperactivity	T1 ADHD index
CHILDREN WITH DS				
T1 Receptive vocabulary	−0.347	−0.533*	−0.261	−0.204
T1 Single word reading	−0.178	−0.404*	−0.235	−0.271
T1 Letter knowledge	−0.338	−0.506*	−0.464*	−0.441*
T1 Rhyme matching	−0.283	−0.422*	−0.282	−0.367
T1 Phoneme matching	−0.536*	−0.263	−0.272	−0.224
T1 Emotional problems	−0.016	0.001	0.185	0.185
T1 Conduct	0.487*	0.198	0.272	0.172
T1 Hyperactivity	0.433*	0.223	0.502*	0.424*
T1 Peer problems	0.139	0.094	−0.123	−0.187
T1 Prosocial behavior	−0.232	−0.536*	−0.035	−0.128
T1 Total difficulties	0.427*	0.224	0.355	0.253
CHILDREN WITH WS				
T1 Receptive vocabulary	0.199	0.280	0.161	0.367
T1 Single word reading	0.265	−0.086	−0.103	−0.006
T1 Letter knowledge	0.285	0.109	0.147	0.195
T1 Rhyme matching	−0.067	−0.067	0.112	0.052
T1 Phoneme matching	0.229	0.074	0.019	0.121
T1 Emotional problems	0.262	0.169	0.275	0.389
T1 Conduct	0.742**	0.469*	0.608**	0.567**
T1 Hyperactivity	0.378	0.737**	0.655**	0.664**
T1 Peer problems	0.236	0.253	0.437*	0.495*
T1 Prosocial behavior	−0.386	−0.038	−0.226	−0.120
T1 Total difficulties	0.571**	0.589**	0.711**	0.762**

*Concurrent correlations between behavioral inattention/hyperactivity (CTRS t-scores) and language/literacy measures (raw scores), as well as socio-behavioral adjustment on the Strengths and Difficulties Questionnaire ("SDQ") for the all groups at Time 1 ("T1"). Where necessary, non-parametric equivalents were also conducted *$p < 0.05$, **$p < 0.001$, areas shaded in gray highlight statistically significant relationships.*

Table 5 | Longitudinal trajectories.

	Time 1		Time 2		Main Effects	
	DS	WS	DS	WS	Time	Group
Receptive vocabulary	30.84 (11.64)	50.81 (58.58)	38.68 (12.09)	58.57 (18.78)	$p < 0.001$	$p < 0.001$
Single word reading	11.3 (16.4)	9.3 (16.4)	19.84 (23.95)	17.81 (21.00)	$p < 0.001$	$p = 0.726$
Letter knowledge	16.36 (8.90)	15.96 (8.74)	21.04 (6.33)	20.12 (7.61)	$p < 0.001$	$p = 0.739$
Rhyme matching (% pass)	9.12 (2.71) (16%)	12.00 (3.68) (56%)	10.00 (3.54) (25%)	13.38 (3.74) (69.2%)	$p = 0.018$	$p = 0.001$
Phoneme matching (% pass)	9.52 (3.02) (16%)	12.41 (9.52) (63%)	10.33 (3.71) (29.2%)	13.08 (3.84) (65.4%)	$p = 0.110$	$p = 0.003$

Mean raw scores (SD) for language and literacy at Time 1 and Time 2 for children with DS and WS. Where necessary, non-parametric statistics and corrections for multiple comparisons were also employed.

significantly to outcomes in literacy and vocabulary a year later.

Following the statistically significant preliminary correlations of the outcome measures at Time 2 with each attention variable at Time 1, hierarchical regression models, entering first the attention variable and then its interaction with group membership coded as a dummy variable as predictors, were built to test whether the two atypically developing groups differed significantly in the extent to which the CTRS variable in question predicted Time 2 vocabulary or literacy. For inattention, the interaction term predicted a significant additional 33.9% of variance in vocabulary, Fchange $(1,44) = 20.215$, $p < 0.001$, supporting the interpretation that individual differences in inattention predicted later vocabulary for children with DS but not WS. The interaction between group and inattention at Time 1 also predicted individual differences (16.4%) in Time 2 rhyme matching, Fchange $(1,42) = 9.254$, $p = 0.004$, and

Table 6 | Longitudinal Pearson correlations.

	T1 Oppositional	T1 Cognitive problems/inattentive	T1 Hyperactivity	T1 ADHD Index
CHILDREN WITH DS				
T2 Receptive vocabulary	−0.386	−0.524*	−0.451*+	−0.390+
T2 Single word reading	−0.189	−0.384	−0.320	−0.270
T2 Letter knowledge	−0.360	−0.364*	−0.539*	−0.485*
T2 Rhyme matching	−0.491*+	−0.578**+	−0.554*+	−0.619**+
T2 Phoneme matching	−0.585**	−0.422*+	−0.436*	−0.427+s
CHILDREN WITH WS				
T2 Receptive vocabulary	0.234	0.227	0.156	0.230
T2 Single word reading	0.168	−0.242	−0.161	−0.091
T2 Letter knowledge	0.067	−0.096	0.058	0.041
T2 Rhyme matching	−0.011	−0.072	0.145	0.148
T2 Phoneme matching	−0.048	−0.089	0.203	0.147

*Longitudinal Pearson's correlations between attention at Time 1 and vocabulary/literacy measures at Time 2 for children with DS or WS. *p < 0.05, **p < 0.01, areas shaded in gray highlight statistically significant relationships; + Relationships between Time 1 attention measures and Time 2 vocabulary/literacy measures that reach significance even after controlling for baseline differences in Time 1 vocabulary/literacy at p < 0.05*

Time 2 phoneme matching, *F*change (1,42) = 6.488, $p = 0.015$ (12.5% of variance). In terms of hyperactivity at Time 1, the interaction predicted significantly 31.4% of variance in Time 2 vocabulary, *F*change (1,43) = 19.94, $p < 0.001$; rhyme matching, *F*change (1,42) = 11.976, $p = 0.001$ (22.1%); and phoneme matching, *F*change (1,42) = 8.664, $p = 0.005$ (17%). The interaction between group and oppositional behavior also predicted phoneme matching *F*change (1,42) = 9.717, $p = 0.003$ (18.3%). Finally, the interaction between ADHD Index and group predicted 23.5% of variance in rhyme matching, *F*change (1,42) = 12.962, $p = 0.001$. None of the other outcome variables were significantly predicted by the interaction effect.

DISCUSSION

The primary aim of this study was to explore the developmental trajectories of the relationship between attentional deficits and the emerging communicative and cognitive domains of vocabulary and reading in two genetically distinct neurodevelopmental disorders. Poor concentration, distractibility, and poor inhibitory control are well-documented behavioral signatures in children with WS and in those with DS (e.g., Cornish and Wilding, 2010; Ekstein et al., 2011; Rhodes et al., 2011b). These attentional profiles are so pervasive that they persist throughout the lifespan (Cornish et al., 2007), are syndrome-specific in terms of their impact on the socio-cognitive end-state (Munir et al., 2000; Scerif et al., 2004), and are likely to increase an already heightened risk of long-term behavioral and emotional problems (Bailey et al., 2008).

In the typically developing literature, converging findings from numerous research studies now clearly attest to the strong association between childhood inattention and poor learning and developmental outcomes, especially in the domain of literacy (Dally, 2006; Smallwood et al., 2007). The extent to which attention plays a similarly critical role in predicting early vocabulary and letter/word skills in children with neurodevelopmental disorders was hitherto unknown.

In the current study, we first contrasted the behavioral ADHD profiles of WS and Down syndrome. Our findings replicated the high levels of ADHD symptomology previously reported separately for both disorders (see Cornish and Wilding, 2010, for review), but they also reveal quite distinct profiles of severity. At first blush, both disorders present with an ADHD index at levels higher than their CA-matched typically developing peers, suggesting some common impact of reduced intellectual level across both disorders. However, at a finer-grained level, we found clear evidence of syndrome-specific signature profiles that indicate that different genetic and/or environmental pathways drive these outcomes. In the WS case, children were markedly more impaired across both the inattention and hyperactive indices, in contrast to children with DS who displayed clinically high levels of inattention symptoms but relatively normal levels of hyperactive symptoms. This latter result was comparable to that of the younger NVMA controls. The ADHD profile we identified in young children with WS is consistent with that recently reported by Rhodes et al. (2011b) who found similar high levels of both inattention and hyperactivity in their sample of older children and adults with WS (mean age 18.4 years), a profile equivalent in severity to that of a developmental matched age sample of children diagnosed with ADHD. Because the DS ADHD profile yields greater inattentive behaviors, their behavioral problems may be missed by clinicians as a result of being less overt. However a potential limitation of the current study is that it utilized teacher only reports of ADHD behaviors. Future studies would benefit from more comprehensive assessments that include both teacher and parent-rated scales alongside well recognized clinical diagnostic tools such as the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000).

The profile of these attention deficits also need to be placed into the broader context of social and peer relations difficulties for children with WS or DS, as those obtained through the SDQ (Goodman, 1997), a measure of broad social adjustment and difficulties. Children with WS and DS differed in their overall profile,

and their attention difficulties on CTRS related differently to peer problems and adjustment. Overall, children with WS experienced greater problems across aspects of socio-behavioral adjustment, including conduct problems, hyperactivity, and peer problems. By contrast, for children with DS, there were fewer significant relationships overall between attention measures on CTRS and strengths and difficulties on SDQ, compared to children with WS for whom all greater problems on all attention subscales related to greater total difficulties.

We then addressed the extent to which syndrome-specific attention profiles related to vocabulary and early literacy indicators, both concurrently and longitudinally. In children with DS, higher levels of inattentive behaviors were related to poorer performance on receptive vocabulary, single word reading, letter knowledge, and rhyme matching but, interestingly, not phoneme matching. In contrast, children with WS showed no relationship between inattentive behaviors and performance on any vocabulary or literacy measures. A year later at Time 2, both groups had improved in overall performance on vocabulary and literacy outcomes but, as in Time 1, attention deficits continued to drive poorer outcomes in the DS group, but not in the WS group. This finding is the first to demonstrate a differential impact of behavioral attention deficits in predicting emerging vocabulary and literacy in two genetically defined neurodevelopmental disorders. In the DS group, the strong association between inattention and vocabulary outcomes parallels that found in the typically developing literature in which inattentive behavior, as observed in everyday settings, can negatively impact on later academic attainment by constraining emergent literacy (Spira and Fischel, 2005; Spira et al., 2005; Smallwood et al., 2007). It is likely that children with DS present with an exaggerated *delay* but in a similar direction to that found in the normal child population. In contrast, children with WS revealed a different pattern in which significant attention deficits exist alongside poor vocabulary and literacy, but with no obvious interrelationship. These (severe) attention difficulties in young children with WS should be the target of intervention, but at least in the age group we targeted, they do not seem to drive the delays in early literacy and vocabulary that we also measured, as indexed by the overall null concurrent and longitudinal correlations. What remains open for further investigation is precisely which socio-cognitive mechanisms may drive early literacy and vocabulary in this group instead, both in terms of compensation and drivers of delay.

Interestingly, relationships more akin to the typical case in DS but not WS are a common pattern found in comparisons of WS and DS in other social and cognitive domains, where DS participants show similar albeit delayed relations to the TD trajectory, whereas those with WS display a deviant developmental trajectory. It is worth recalling that none of the genes are mutated in DS; the trisomy gives rise to over-expression of gene products which might compromise the computational system in more general ways. By contrast, while WS is characterized by deletion of one copy of some 28 genes on chromosome 7, it is the haploinsufficiency of four specific genes at the telomeric end of the deletion that appear to give rise to more specific vulnerabilities for socio-cognitive functions.

Taken together, our data clearly indicate that general-purpose intervention programs are inadequate for neurodevelopmental disorders and that basic research identifying syndrome-specific developmental trajectories must underpin syndrome-specific training programs, if we are to help children with genetic disorders reach their full potential.

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Social communication and theory of mind in boys with autism and fragile X syndrome

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Impairments in the social use of language, or pragmatics, constitute a core characteristic of autism. Problems with pragmatic language have also been documented in fragile X syndrome (FXS), a monogenic condition that is the most common known genetic cause of autism. Evidence suggests that social cognitive ability, or theory of mind, may also be impaired in both conditions, and in autism, may importantly relate to pragmatic language ability. Given the substantial overlap observed in autism and FXS, this study aimed to better define those social-communicative phenotypes that overlap in these two conditions by comparing pragmatic language ability and theory of mind in children with idiopathic autism and children with FXS, with and without autism, as well as children with Down syndrome and typically developing controls. We further examined correlations between these cognitive-behavioral phenotypes and molecular genetic variation related to the Fragile X Mental Retardation-1 gene (*FMR1*) in the FXS group. Results indicated that children with idiopathic autism and those with FXS and autism performed comparably on direct-assessment measures of pragmatic language and theory of mind, whereas those with FXS only did not differ from controls. Theory of mind was related to pragmatic language ability in all groups. Pragmatic language and theory of mind also correlated with genetic variation at the *FMR1* locus (Cytosine-Guanine-Guanine repeats and percent methylation). These results point toward substantial overlap in the social and language phenotypes in autism and FXS and suggest a molecular genetic basis to these phenotypic profiles.

Keywords: autism, fragile X syndrome, pragmatic language, social communication, theory of mind

Autism and fragile X syndrome (FXS) are genetically based neurodevelopmental disorders that share a number of cognitive and behavioral characteristics, including impairments in social communication, or pragmatic language. Pragmatic language is a complex skill grounded deeply in the capacity to apprehend and contend with social information. Mastering pragmatic language skills (e.g., politeness strategies, adopting different registers, or styles of communication depending upon addressee, conversational, and narrative practices, etc.) hinges on the ability to anticipate others' interests, infer the background knowledge brought by each interlocutor to the communicative interaction, monitor participants' involvement, and appreciate cultural conventions for social and communicative interaction (Grice, 1975; Brown and Levinson, 1987; Sperber and Wilson, 2002; Wilson and Sperber, 2004). Such abilities may be considered aspects of social cognition or "theory of mind," namely, the ability to attribute thoughts, emotions, beliefs, and desires to others, and to appreciate that others may hold thoughts and feelings that are different than one's own. Important evidence for the role of theory of mind in pragmatic language ability has come from studies of autism, where autistic groups' theory of mind difficulties appear strongly associated with the pragmatic language impairments observed in this population (Loveland and Tunali, 1993; Tager-Flusberg and Sullivan, 1995; Surian et al., 1996; Capps et al., 1998, 2000; Tager-Flusberg, 2000; Losh and Capps, 2003). Ultimately, such findings from neurogenetic populations may provide clues to the brain and gene basis of complex human traits such as social communication and theory of mind, by providing links between gene, brain, and behavior. In other words, characterizing pragmatic language impairments in autism and related neurogenetic disorders such as FXS could help to clarify how underlying genetic variation and resultant changes in brain development might give rise to specific phenotypes such as pragmatic language or theory of mind impairment.

Whereas the genetic basis of autism is complex, with the disorder still defined behaviorally (American Psychiatric Association, 1994), FXS is a monogenic X-linked disorder that is the most common inherited cause of intellectual disability (ID) and the most common known genetic cause of autism. Because FXS is more etiologically homogeneous than idiopathic autism, careful study of autism-related phenotypes in the context of this single-gene disorder can provide an important avenue for identifying pathophysiological mechanisms underlying the symptoms of autism, and informing the genetic basis of complex human skills such as pragmatic language and theory of mind.

In this study, we compared pragmatic language ability in children with idiopathic autism and children with FXS, with and without autism, in order to better define those social-communicative phenotypes that overlap in these two conditions. We further

examined theory of mind in these groups, both to characterize groups' abilities and to determine whether there exists phenotypic overlap in this important domain, as well as to examine theory of mind as a potential underpinning factor in the pragmatic language impairments in each group. As noted, strong links have been documented between pragmatic language impairment and theory of mind in autism, but to our knowledge, these relationships have not yet been studied in FXS. Finally, we examined molecular genetic correlates of pragmatic language and theory of mind in the FXS group, with the goal of detecting gene-behavior associations that may have implications for the genetic basis of social communication and theory of mind. Below we present a brief review of FXS and rationale for comparison of pragmatic language and theory of mind in autism and FXS.

INTRODUCTION TO FXS AND ITS OVERLAP WITH AUTISM

Fragile X syndrome is the most frequent known hereditary cause of ID (Dykens et al., 2000; Hagerman and Hagerman, 2002), with the full mutation estimated to occur in approximately 1 in 2,500 to 1 in 5,000 individuals (Hagerman, 2008; Coffee et al., 2009; Fernandez-Carvajal et al., 2009). On the X chromosome, an expansion of Cytosine-Guanine-Guanine (CGG) repeats in the Fragile X Mental Retardation-1 gene (*FMR1*) results in methylation (i.e., shutting down) of the gene and reduced or absent production of the Fragile X Mental Retardation Protein (FMRP). FMRP is thought to be critical for typical brain development (Devys et al., 1993; Jin and Warren, 2003), and its deficiency in FXS is believed to underlie the physical and cognitive-behavioral characteristics of the syndrome. Males with FXS typically experience moderate or severe ID (Bennetto and Pennington, 2002; Abbeduto and Chapman, 2005) and more severe impairments than females overall, because females possess one unaffected X chromosome in addition to one affected chromosome (Hagerman and Hagerman, 2002; Loesch et al., 2003; Reiss and Dant, 2003; Bailey et al., 2008, 2009). Commonly co-occurring conditions include social anxiety (Bregman et al., 1988; Hagerman, 2002; Cordeiro et al., 2011), attentional deficits (Hooper et al., 2000; Wilding et al., 2002), and autism (Hagerman and Hagerman, 2002).

Autistic characteristics observed in individuals with FXS include stereotypic and repetitive behaviors, poor eye contact, and social avoidance (Reiss and Freund, 1992; Hagerman and Hagerman, 2002). FXS is the most common known single-gene disorder linked to autism (Hagerman and Hagerman, 2002). Results of studies using gold standard diagnostic measures indicate that 20–50% of males with FXS may also have autism and as many as three-quarters may meet ASD criteria (Rogers et al., 2001; Kaufmann et al., 2004; Philofsky et al., 2004; Clifford et al., 2007; Hall et al., 2008). In addition, approximately 2–6% of individuals with autism test positive for the fragile X mutation (Hagerman, 2006).

Language development is impaired in males with FXS beyond expectations for cognitive level, with greater deficits in language production compared with comprehension (Roberts et al., 2001, 2008; Abbeduto et al., 2007; Finestack et al., 2009). Early investigations of pragmatic language in FXS reported poor topic maintenance with inappropriate responses, rambling, automatic phrases, and perseveration or repetitive language (Hanson et al., 1986; Madison et al., 1986). However, these studies included small samples and lacked comparison groups. Compared with controls with typical development or Down syndrome (DS), males with FXS have greater difficulty maintaining topics of conversation and produce more off-topic or tangential contributions to the topic (Wolf-Schein et al., 1987; Sudhalter and Belser, 2001) as well as more perseveration (Wolf-Schein et al., 1987; Sudhalter et al., 1990; Roberts et al., 2007a). Young individuals with FXS may also be less likely than MA-matched typically developing (TD) children to report actions during story retelling (Estigarribia et al., 2011) and to request clarification or additional information in the face of unclear messages from a communication partner (Abbeduto et al., 2008). Compared with individuals with idiopathic autism, males with FXS without autism produced more turns per topic and less echolalia but more perseveration in one study (Sudhalter et al., 1990).

Autism status of participants with FXS was handled differently across the studies reviewed above – individuals with FXS and comorbid autism were either excluded (Sudhalter et al., 1990; Abbeduto et al., 2008), included as a separate group (Roberts et al., 2007a; Estigarribia et al., 2011), or autism status was not reported (Hanson et al., 1986; Madison et al., 1986; Wolf-Schein et al., 1987; Sudhalter and Belser, 2001). Several studies have directly examined the role of autism in language in FXS. On global language assessments, males with FXS and comorbid autism show more severe language deficits than males without autism (Bailey et al., 2001; Rogers et al., 2001; Philofsky et al., 2004). Findings are more mixed with respect to specific language domains, however. In several studies, groups of males with FXS did not differ by autism status in either receptive or expressive vocabulary (Price et al., 2007; Roberts et al., 2007a; Kover and Abbeduto, 2010; McDuffie et al., 2012) or syntax (Price et al., 2007, 2008; Kover and Abbeduto, 2010; McDuffie et al., 2012). However, individuals with FXS and comorbid autism performed more poorly than those with only FXS in receptive vocabulary and syntax in one study (Lewis et al., 2006), and autism severity may be negatively related to receptive vocabulary skill when a continuous analytical approach is taken (McDuffie et al., 2012). In two studies, boys with both FXS and autism did not differ from those without autism but did differ from TD controls (whereas boys with only FXS did not) in expressive vocabulary (Roberts et al., 2007b) and overall story retelling ability (Estigarribia et al., 2011), perhaps suggesting that autism in FXS negatively impacts these language areas as well. Boys with FXS and comorbid ASD have been shown to produce more off-topic or tangential language than boys with only FXS (Roberts et al., 2007a). Children and adolescents with both FXS and autism were also rated higher than those without autism in the current use of stereotyped utterances/delayed echolalia and reciprocal conversation on the Communication domain of the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994) in another recent study (McDuffie et al., 2010).

THEORY OF MIND IN FXS

For the most part, theory of mind performance in FXS appears to be on par with cognitive expectations, and children with FXS score comparably to children with DS or ID of unknown etiology (Mazzocco et al., 1994; Garner et al., 1999; Cornish et al., 2005). Children with FXS also perform similarly on false belief

theory of mind tasks to younger, non-verbal mental age-matched TD children (Abbeduto et al., 2001). However, some studies have reported theory of mind deficits in FXS that cannot be explained by cognitive impairment. In a recent comparison of 30 boys with FXS to 15 boys with unspecified ID, Grant et al. (2007) found poorer overall performance on standard false belief tasks among the FXS group (Grant et al., 2007). Similar findings were reported by Garner et al. (1999), who found that a small group of eight boys with FXS performed significantly worse than a matched ID group on a deceptive box false belief task, although these findings may have been sporadic as no group differences were detected on a secondary false belief task (the Sally–Anne task), nor on a second-order false belief task (Garner et al., 1999).

A few studies have examined the impact of autism comorbidity on theory of mind abilities in FXS syndrome, and suggest that autism status may play a role in theory of mind ability in FXS. Lewis et al. (2006) compared non-verbal IQ-matched groups of children with FXS with and without comorbid autism, and found that the children with FXS who met criteria for autism showed worse performance on false belief tasks, despite similar cognitive ability (Lewis et al., 2006). The study by Grant et al. (2007) failed to detect differences in false belief performance among children with FXS with and without autism, although there was a non-significant trend toward poorer performance in the comorbid autism group (Grant et al., 2007).

RATIONALE FOR THE PRESENT STUDY

In spite of considerable overlap between autism and FXS, and evidence that both disorders are characterized by difficulties in pragmatic language, and likely theory of mind as well (at least in those individuals with comorbid FXS and autism), few direct population comparisons exist to allow precise comparison of these populations and drawing ties between known underlying genetic variation and the social phenotypes of interest. Additionally, whether impairments in pragmatic language and theory of mind may be related in both populations is not known. This study addressed these questions by comparing pragmatic language ability and theory of mind in children with idiopathic autism, children with FXS with and without autism, children with DS (included as a comparison group to control for general cognitive delays), and TD children. Further, correlations with genetic variation at the *FMR1* locus were examined to inform the potential genetic underpinnings of pragmatic language and theory of mind profiles observed.

MATERIALS AND METHODS

PARTICIPANTS

Study participants were 28 boys with idiopathic autism (autism only; ASD-O), 40 boys with both FXS and ASD (FXS-ASD), 21 boys with FXS only (FXS-O), 21 boys with DS, and 20 TD boys participating in a large-scale longitudinal study of speech, language, and social-behavioral profiles in children with neurodevelopmental disabilities. Boys with autism, FXS, and DS were recruited from the Research Participant Registry Core of the Carolina Institute for Developmental Disabilities (CIDD) at the University of North Carolina at Chapel Hill (UNC), genetic clinics, and parent support groups in the Southeastern, Eastern, and Midwestern U.S. TD boys were recruited through the CIDD Participant Registry Core, schools, and childcare centers in North Carolina. Study procedures were approved by the institutional review boards at UNC and Northwestern University.

Participants included only boys since females with FXS are less severely impaired than males (Hagerman and Hagerman, 2002; Loesch et al., 2002) and less likely to have autism (Clifford et al., 2007; Bailey et al., 2008). Upon enrollment, parents reported that all boys were combining three or more words. For all children, English was the primary language spoken in their homes. A composite score of Peabody Picture Vocabulary Test-Third Edition (PPVT-III; Dunn and Dunn, 1997) and Expressive Vocabulary Test (EVT; Williams, 1997) raw scores was used to match groups on receptive and expressive lexical skills to help ensure that any differences detected in social communication and theory of mind were not due to differences in structural language ability (see below for description of vocabulary measures and **Table 1** for group means and standard deviations). Pairwise *t*-tests indicated no significant differences between groups (all p between 0.09 and 0.85, with the comparisons between DS vs. FXS-O and TD as well as between FXS-ASD vs. TD with $p > 0.30$). Age equivalent scores from both measures were included as covariates in all statistical models. All boys with FXS had a diagnosis of the full mutation. Boys were excluded for having an average hearing threshold greater than 30 dB HL in the better ear, determined from a hearing screening across 500; 1,000; 2,000; and 4,000 Hz with a MAICO MA 40 audiometer. Boys with DS and TD were screened for autism with the Social Communication Questionnaire (SCQ; Rutter et al., 2003) and also subsequently excluded for scoring as "autism" or "autism spectrum" on the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2001), described below. **Table 1** provides background characteristics of participants in each group.

ASSESSMENTS

Boys were tested in a quiet space in a school, home, or in a laboratory setting. The full assessment lasted approximately 4–6 h, with several breaks to prevent fatigue. Assessments were video-recorded with a Sony Digital8 video camera (Model DCR-TVR27) and audio-recorded with a Marantz portable solid-state recorder (PMD670).

Autism classification

The ADOS (Lord et al., 2001) was used to confirm autism in boys with ASD-O and to classify boys with FXS according to autism status. The ADOS consists of developmentally appropriate activities that are structured to provide a child with opportunities to show diagnostic symptoms of autism, and yields classifications of "autism," "spectrum," and "no autism." Trained examiners coded administrations from video, with scoring based on the revised algorithms (Gotham et al., 2007, 2008). Coders included one research assistant who was reliable with an independent ADOS trainer, and one coder who was reliable with the aforementioned research assistant. Twenty-four boys with ASD-O were identified by the ADOS as having "autism" and three as having "spectrum." One additional boy with ASD-O did not meet criteria for autism or spectrum on the ADOS, scoring 6 (ASD cutoff is 7). However, because his scores on the Autism Diagnostic Interview – Revised (Lord et al., 1994) all exceeded diagnostic cutoffs and medical

Table 1 | Group characteristics.

	ASD-O *N* = 28	FXS-ASD *N* = 40	FXS-O *N* = 21	DS *N* = 21	TD *N* = 20
	Mean (SD) (Range)	**Mean (SD) (Range)**	**Mean (SD) (Range)**	**Mean (SD) (Range)**	**Mean (SD) (Range)**
Chronological age	9.21 (2.22) (4.16–12.74)	10.55 (2.42) (6.58–15.07)	9.61 (3.03) (6.06–14.98)	10.86 (2.07) (6.81–14.86)	4.84 (1.34) (3.23–8.78)
Non-verbal mental age[1]	5.88 (1.32) (3.92–10.50)	5.02 (0.49) (3.50–6.00)	5.44 (0.95) (4.42–8.25)	5.33 (0.83) (4.33–8.25)	5.49 (1.45) (3.58–9.17)
Expressive vocabulary age[2]	5.62 (1.59) (3.42–8.92)	4.99 (0.99) (2.67–7.25)	5.42 (1.56) (2.75–9.25)	5.41 (1.30) (3.58–8.58)	5.87 (2.14) (2.92–12.33)
Receptive vocabulary age[3]	5.76 (1.81) (3.08–10.00)	5.67 (1.39) (2.42–8.83)	6.36 (2.55) (3.42–13.83)	5.18 (1.44) (2.42–7.50)	6.12 (2.01) (2.17–11.58)
Mean length of utterance (morphemes)	4.18 (0.94) (2.22–5.49)	3.49 (0.69) (2.18–4.88)	3.98 (0.74) (2.27–4.74)	3.14 (0.75) (1.76–4.76)	4.87 (0.54) (4.12–6.05)

[1] *Leiter-R, age equivalent in years.*

[2] *Expressive Vocabulary Test (EVT), age equivalent in years.*

[3] *Peabody Picture Vocabulary Test – 3rd Edition (PPVT-III), age equivalent in years.*

records confirmed a clinical diagnosis by an independent diagnostician, he was not dropped from analyses. Thirty-three boys with FXS were identified by the ADOS as having "autism," seven as having "spectrum," and 21 as having "no autism." Those meeting criteria for either autism or spectrum formed the group of boys with FXS-ASD.

Pragmatic language

The participants' pragmatic language skills were assessed with the Pragmatic Judgment subtest of the Comprehensive Assessment of Spoken Language (CASL; Carrow-Woolfolk, 1999) and the Children's Communication Checklist-Second Edition, U.S. Edition (Bishop, 2006). The Pragmatic Judgment subtest is a direct-assessment tool for examining general pragmatic language understanding and use. The examiner reads aloud a script representing a particular part of daily life, and children are either asked to judge the appropriateness of language used in a particular situation, or they are asked to provide a pragmatically appropriate response. Test-retest reliability coefficients for the Pragmatic Judgment subtest for the age ranges included in this study exceed 0.80, suggesting that this subtest is a reliable index of pragmatic language skill. Age equivalents were computed for the current study except in the case of a raw score of 0, which for analysis was considered missing. Four boys with ASD-O, two boys with DS, and one boy with FXS-ASD received a raw score of 0.

The CCC-2 was developed to measure social language use (although it also assesses structural language domains), and requires parents and/or teachers to rate a variety of communication difficulties or strengths according to how often the behavior in question is observed in everyday settings. For this study, teacher ratings were used. The checklist includes 70 items and yields 10 scaled scores. The scales of primary interest for pragmatic language assessment included the following: Initiation, Scripted Language, Context, Non-verbal Communication, Social Relations, and Interests. We also compared the Speech, Syntax, Semantics, and Coherence scales as variables of secondary interest. Scaled scores range from 1 to 19, with a higher value indicating better communication. The General Communication Composite (GCC) standard score was also calculated (ranging from 40 to 160) and based on the sum of 8 scaled scores (all except Social Relations and Interests).

Theory of mind

Theory of mind was assessed using one of two comparable batteries of tasks. The first version included the following tests: Perspective Taking, Diverse Desires, Diverse Belief, False Belief, Knowledge Access, and Explicit False Belief (Wellman and Liu, 2004; Slaughter et al., 2007). This version involved more complex, primarily verbal, presentation of the tasks. Results from initial assessments indicated that the tasks in the original battery were too difficult for some lower functioning children, and that the heavy verbal load impacted performance above and beyond children's levels of social cognitive competence. Thus, more basic tasks assessing intentionality and understanding of desires were added to the battery (detailed below), and administration of the false belief tasks was also modified such that scenarios were enacted, rather than read as a story involving abstract characters, to decrease verbal and cognitive load (Flavell et al., 1983; Lewis and Mitchell, 1994; Repacholi and Gopnik, 1997; Matthews et al., 2003; Slaughter et al., 2007). It was not necessary to alter the Perspective Taking Task as the protocol was already interaction-based. Two, more basic, tasks were added to tap metarepresentational skills in children who were not capable of performing the original, more advanced battery – Simple Desires and Appearance-Reality – which have been used with children as young as 14 months and 3 years, respectively, and are described in the Appendix. Each participant received either the original or the modified battery of tasks, depending on when

they were tested. All assessments were second-scored by a trained research assistant. See Appendix for further task description and scoring procedures.

To produce a single composite theory of mind score for all children (and ensure comparability across the initial and modified batteries), factor analysis scores were derived. First, the two batteries were tested in separate confirmatory factor analytic (CFA) models. Both factor models were estimated under weighted least squares using MPlus (Muthen and Muthen, 2006). The commonality of the Perspective Taking Task across both batteries provided an anchor that enabled us to ensure score equivalence across forms. This task was used to set the metric for the latent variable. The CFA for the older battery was run first. In the model of the newer battery, we fixed the factor loading and threshold parameters for the Perspective Taking Task to be equal to those parameters from the model of the older battery. Thus, estimates of the latent variable, theory of mind, were equivalent across both models. That is, a given respondent would be expected to receive the same score regardless of which form of the test he or she was given. Results indicated very good model fit for the one factor solution in both models (older form: RMSEA = 0.003, CFI = 1.00; newer form: RMSEA = 0.000, CFI = 1.00). Finally, we used the factor models to estimate and export theory of mind scores for each individual. To aid in interpretability, these scores were then standardized to have a mean of 10 and a standard deviation of 1.

Non-verbal cognitive ability

Non-verbal cognition was assessed with the Brief IQ composite of the Leiter-R (Roid and Miller, 1997), which includes Sequential Order, Figure Ground, Form Completion, and Repeated Patterns subtests. Age equivalents were calculated based on the published norms.

Structural language

Receptive vocabulary, expressive vocabulary, and expressive syntax were measured with the Peabody Picture Vocabulary Test-Third Edition (PPVT-III; Dunn and Dunn, 1997), EVT (Williams, 1997), and mean length of utterance (MLU; Brown, 1973), respectively. Age equivalents for the PPVT-III and EVT were calculated according to published norms. MLU in morphemes was calculated from 100 child utterances produced during the ADOS. The language samples were transcribed using Systematic Analysis of Language Transcripts (SALT) software conventions (Miller and Chapman, 2008) and using ELAN transcription software (Max Planck Institute for Psycholinguistics, 2002; Sloetjes and Wittenburg, 2008), which allowed transcribers to sync visual information from video recording with separate high-quality audio recordings. All transcribers achieved 80% reliability against two gold standard transcripts for each diagnostic group prior to transcribing samples for the present study. A random subset of the transcripts (10% or more from each group) was independently transcribed by a second research assistant, and morpheme-to-morpheme agreement between the original and reliability transcripts was 77% overall.

Molecular profile characterization in FXS

Measures of *FMR1*-related variation were derived from blood samples and included the number of CGG expansion repeats, percentage of gene methylation, and percentage of lymphocytes producing FMRP. The number of CGG expansion repeats was determined using PCR analysis to determine repeat size and Southern blot to confirm PCR results for expanded alleles. Phosphorimaging was performed to determine percent methylation. Blood smears were analyzed by immunocytochemistry to determine FMRP expression. The majority of blood samples (85%) were analyzed by Kimball Genetics, Inc., with remaining analyses completed by one of several other laboratories.

DATA ANALYSIS

Group Comparisons

Between group differences in pragmatic language (indexed by the Pragmatic Judgment subtest of the CASL and select scales of the CCC-2) were examined using analysis of covariance (ANCOVA) models, with the following covariates: age equivalent scores for receptive and expressive vocabulary measured by the PPVT-III and EVT, respectively; MLU; and general cognitive ability measured by the Leiter-R. Planned *post hoc* contrasts were used to test for specific between group differences. Group differences in theory of mind were also examined with diagnosis as the primary predictor and PPVT-III, EVT, MLU, and Leiter-R included as covariates.

Given the large number of models, omnibus *F*-tests were adjusted using the Benjamini and Hochberg (1995) procedure to control for false discovery.

Genetic correlates of pragmatic language and theory of mind in FXS groups

Simple correlations were run with the FXS group as a whole (to increase power), between the genetic variables and measures of structural language (PPVT-III, EVT, MLU, and structural language subscales of the CCC), general cognition (Leiter-R), pragmatic language (CASL and pragmatic language subscales of the CCC-2), and theory of mind. Because the number of CGG expansion repeats and percent methylation were highly skewed, these variables were log-transformed prior to analyses.

RESULTS

GROUP COMPARISONS OF PRAGMATIC LANGUAGE

Comparisons of group performance on the Pragmatic Judgment subscale of the CASL, controlling for structural language and general cognitive abilities, were statistically significant, $F(4, 108) = 5.49$, $p < 0.001$. *Post hoc* tests (see **Figure 1**) indicated that the ASD-O group scored lower than the FXS-O (d[1] = 0.64), DS ($d = 0.41$), and TD ($d = 0.69$) groups ($ps < 0.05$). The FXS-ASD group showed a similar pattern, with significantly lower scores than both FXS-O ($p = 0.021$, $d = 0.35$) and TD groups ($p = 0.029$, $d = 0.41$), but did not differ significantly from the DS group ($p = 0.403$). The ASD-O and FXS-ASD groups performed comparably ($p = 0.100$).

Model tests and adjusted means are presented in **Table 2** for the subscales of the CCC-2. The models for the Social Relations and Interests subscales were not significant, and *post hoc* comparisons are therefore not presented for these subscales. Significant group differences were detected for all other subscales.

[1]Cohen's *d* (Cohen, 1988) is a measure of effect size where 0.2 is considered small, 0.5 is considered medium, and 0.8 is considered large.

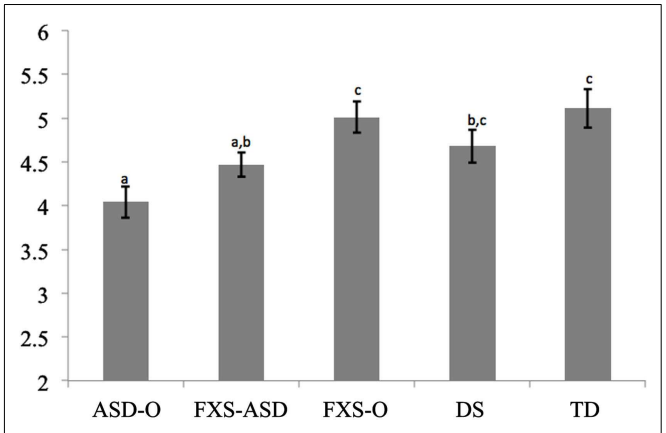

FIGURE 1 | Model Adjusted Pragmatic Judgment Scores on the CASL. Notes: groups not sharing superscripts are significantly different from each other ($p < 0.05$). F for Diagnosis (4, 107) = 4.39, $p < 0.001$.

The TD group scored significantly higher on the CCC-2 total score than all other groups (all $d > 1.4$) with no other between group differences. This pattern was repeated for the Syntax, Semantics, Coherence, Scripted Language, and Context subscales (all d for the comparison with TD > 1.3). On the Speech subscale, the DS group also had significantly lower scores than both the ASD-O ($d = 0.34$) and FXS-O ($d = 0.76$) groups, but was not different from children with FXS-ASD. TD children had higher speech scores than all other groups (all d for the comparison with TD > 1.3). The FXS-ASD group scored lower than both the DS ($d = 0.65$) and ASD-O ($d = 0.71$) groups on the Initiation subscale, with TD boys scoring higher than all groups but ASD-O (all d for the significant comparisons with TD > 0.70). The pattern of means was most notably different for the Non-verbal Communication subscale. This was the only outcome, other than Social Relations and Interests, where the DS sample did not score significantly lower than the TD sample. The TD group scored significantly higher in non-verbal communication than the ASD-O, FXS-ASD, and FXS-O groups.

THEORY OF MIND AND PRAGMATIC LANGUAGE

Comparing scores on the battery of theory of mind tasks, which were standardized to have a mean of 10 and a standard deviation of 1, covarying language and cognitive ability indicated that the TD group performed better than ASD-O, FXS-ASD, and DS groups (all $d > 0.70$). The difference between TD and FXS-O approached significance ($p = 0.082$, $d = 0.56$). There were no other significant group differences (see **Figure 2**).

Significant correlations between theory of mind and performance on the CASL Pragmatic Judgment subscale were found for all groups (see **Table 3**). Theory of mind was additionally related to the "Initiation" subscale of the CCC-2 in the autism group ($r = 0.56$, $p < 0.05$) and in the FXS group, it was related to the CCC-2's "Coherence" subscale ($r = 0.36$, $p < 0.01$).

MOLECULAR GENETIC CORRELATES OF PRAGMATIC LANGUAGE IN FXS

Correlations were conducted to examine potential associations between molecular genetic variables (CGG repeat number, FMRP,

Table 2 | Model adjusted scores on pragmatic language and general language subscales of the CCC-2.

Group	Scripted language	Initiation	Non-verbal communication	Social relations	Interests	Context	Speech	Syntax	Semantics	Coherence	CCC-2	
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)	Standard Score
ASD-O	5.43 (0.78)^{a}	7.46 (0.76)^{a,c}	4.76 (0.72)^{a}	5.46 (0.71)	6.22 (0.89)	5.09 (0.65)^{a}	5.97 (0.89)^{a}	5.09 (0.75)^{a}	6.78 (0.65)^{a}	4.49 (0.77)^{a}	73.56 (3.95)^{a}	
FXS-ASD	5.50 (0.58)^{a}	4.91 (0.56)^{b}	4.45 (0.54)^{a}	6.31 (0.54)	6.90 (0.66)	4.80 (0.47)^{a}	4.28 (0.65)^{a,b}	4.33 (0.55)^{a}	5.16 (0.49)^{a}	3.98 (0.55)^{a}	67.94 (2.85)^{a}	
FXS-O	4.90 (0.68)^{a}	6.21 (0.63)^{a,b}	4.55 (0.61)^{a}	6.76 (0.59)	8.01 (0.72)	5.23 (0.54)^{a}	5.77 (0.74)^{a}	4.94 (0.64)^{a}	5.50 (0.55)^{a}	4.66 (0.62)^{a}	69.64 (3.29)^{a}	
DS	6.70 (0.74)^{a}	6.87 (0.76)^{a}	6.10 (0.70)^{a,b}	6.98 (0.68)	7.52 (0.85)	5.71 (0.64)^{a}	3.06 (0.85)^{b}	3.80 (0.72)^{a}	5.73 (0.64)^{a}	4.60 (0.69)^{a}	72.65 (3.81)^{a}	
TD	9.90 (0.85)^{b}	9.48 (0.83)^{c}	7.86 (0.79)^{b}	7.31 (0.77)	10.15 (0.97)	9.56 (0.70)^{b}	9.63 (0.97)^{c}	9.13 (0.81)^{b}	9.07 (0.73)^{b}	9.28 (0.80)^{b}	96.63 (4.08)^{b}	
F for Diagnosis	(3, 63) = 6.36**	(3, 63) = 4.73*	(3, 64) = 4.16**	(3, 62) = 1.16	(3, 63) = 2.97	(3, 63) = 8.80**	(3, 64) = 6.45**	(3, 63) = 6.74**	(3, 64) = 4.77**	(3, 60) = 8.15**	(3, 57) = 8.58**	

Groups not sharing superscripts within a column are significantly different from each other ($p < 0.05$).
*$p < 0.05$, **$p < 0.01$.*

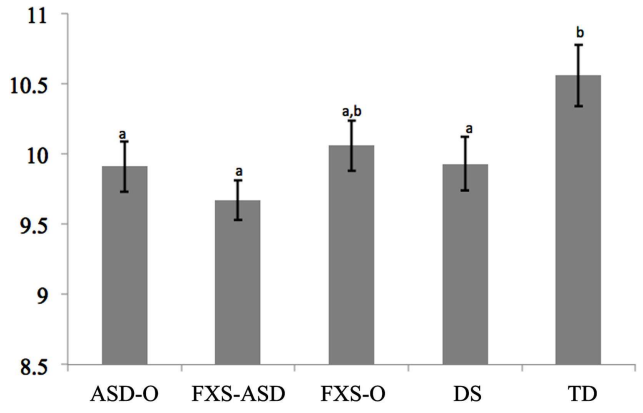

FIGURE 2 | Model Adjusted Theory of Mind Scores. Notes: groups not sharing superscripts are significantly different from each other ($p < 0.05$). F for Diagnosis (4, 106) = 2.87, $p < 0.05$.

Table 3 | Correlations between theory of mind and pragmatic language on the CASL.

	Theory of mind			
	ASD-O	**FXS (all)**	**DS**	**TD**
CASL pragmatic judgment	0.56*	0.36**	0.51*	0.54**
age equivalent (*n*)	21	57	21	19

*$p < 0.05$, **$p < 0.01$.

and percent methylation) and measures of structural language (PPVT-III, EVT, MLU, and relevant subscales of the CCC-2), general cognition (Leiter-R), pragmatic language (Pragmatic Judgment on the CASL, and the pragmatic language subscales of the CCC-2), and theory of mind. Because CGG repeat numbers and methylation values were very skewed, these variables were log-transformed prior to analysis. **Table 4** presents these results, with the exception of the CCC-2, where no significant correlations were detected. No significant associations were observed with FMRP, but higher CGG repeat numbers and increased methylation were associated with lower CASL pragmatic judgment scores. Increased methylation was also significantly related to poorer theory of mind. Measures of structural language and general cognition also showed some relationship with CGG repeat length and methylation.

DISCUSSION

By comparing the pragmatic language abilities of children with idiopathic autism or FXS (both with and without autism), with children with DS and TD children, this study aimed to determine the extent to which pragmatic language impairment may overlap in autism and FXS, and may potentially be tied to underlying molecular genetic variation related to *FMR1*, the gene that causes FXS. Additionally, we explored theory of mind ability as a potential correlate of pragmatic language across groups. Prior studies have reported a link between impaired theory of mind and pragmatic

Table 4 | Genetic correlations with language (structural and pragmatic language), general cognition, and theory of mind in the FXS group.

	CGG Repeats	**Log-transformed FMRP**	**Log-transformed percent methylation**
PPVT	−0.33*	0.33	−0.32
n	36	33	33
EVT	−0.11	0.31	−0.41*
n	36	33	33
Leiter	−0.36*	0.34	−0.30
n	36	33	33
MLU	−0.35*	0.10	−0.34
n	36	32	32
CASL Pragmatic judgment	−0.40*	0.33	−0.36*
(*n*)	36	33	33
Theory of mind	−0.32	0.24	−0.45*
n	35	33	32

*$p < 0.05$.

language use in autism, but to our knowledge this question has not yet been addressed in FXS.

Results indicated that the ASD-O and FXS-ASD groups looked quite similar on direct-assessment of pragmatic language using the CASL, with both groups performing more poorly than the FXS-O, DS, and TD groups. Yet on teacher report findings were more divergent (e.g., Initiation, where the FXS-ASD group scored significantly lower than the ASD-O group). It could be the case that a global measure of pragmatic language ability such as the CASL obscures actual differences between these groups. Alternatively, informant-based methods such as the CCC-2 may introduce measurement error that complicates group comparisons (e.g., different teachers may have different thresholds for ratings, based on their prior experience, the composition of their classrooms, etc.). Further research comparing these groups using direct-assessment measures of specific types of pragmatic language ability will be valuable in addressing this question and determining the extent of overlap in pragmatic language impairment in autism and FXS.

Analyses of theory of mind ability revealed patterns of performance quite similar to those observed in the CASL test of pragmatic language – the ASD-O and FXS-ASD groups performed most poorly, and children with FXS-O did not differ significantly from controls. In this case, however, the DS group performed more like the ASD-O and FXS-ASD groups. We also found that theory of mind ability was associated with pragmatic language on the CASL for all groups, where better theory of mind scores were associated with more pragmatic language competence. Although we cannot draw definitive causal conclusions from the present data, these findings certainly support the hypothesis that the ability to understand and predict one's own and others' thoughts, feelings, intentions, and desires is a critical skill underpinning competent pragmatic language use (Sperber and Wilson, 2002; Wilson and

Sperber, 2004). When theory of mind is impaired, as was the case for the ASD-O and FXS-ASD groups, children may be ill equipped to contend with the demands of social discourse, and less apt to glean information necessary for developing pragmatic language skills. Such a relationship has been demonstrated across a range of pragmatic language skills in autism (Loveland and Tunali, 1993; Tager-Flusberg and Sullivan, 1995; Surian et al., 1996; Capps et al., 1998, 2000; Tager-Flusberg, 2000), and our findings suggest a similarly important role in the pragmatic language problems observed in a subgroup of children with FXS who show pragmatic language impairments as well. That significant associations were detected in all groups, even those who did not show significant pragmatic language impairment, may demonstrate the important role of theory of mind in supporting more fluent pragmatic language use as well. It is of course also possible that theory of mind tasks and pragmatic language are tapping some additional mediating (or moderating) abilities.

Patterns observed in the FXS-O and DS groups may also be informative, particularly with regard to defining syndrome-specific language and social cognitive profiles across these different groups. In particular, whereas social skills are generally considered to represent a relative strength in individuals with DS, the literature on pragmatic language in DS is actually quite mixed, with documented challenges compared with MA-matched TD children including initiation and elaboration of topics (Tannock, 1988; Roberts et al., 2007a), initiation of communicative repairs (Abbeduto et al., 2008), and clarity of messages (Abbeduto et al., 2006). Thus, our finding that boys with DS performed comparably to boys with FXS-ASD is not necessarily surprising. On the otherhand, we may have found significant differences between FXS-ASD and DS groups with a larger sample size or if we examined particular aspects of pragmatic language with direct-assessment measures (and it is important to note that the DS group did not differ significantly from the TD group, whereas the FXS-ASD group did perform significantly more poorly than the TD group). Thus, interpretation of these similarities with the present data is not straightforward.

In the FXS-O group, these data indicated that pragmatic language and theory of mind were relative strengths, and deficits in these areas may be restricted only to those with FXS-ASD, suggesting that pragmatic language deficit (or theory of mind) is not a core characteristic of FXS but rather autism in FXS. This is consistent with findings from Roberts et al. (2007a), who found that boys with FXS-O did not produce more non-contingent language than TD boys, but that the FXS-ASD group produced more non-contingent language than both of these groups. However, it is important to note that the difference between the TD and FXS-O groups approached significance so may have revealed true differences with a larger sample.

Though not a primary focus of the current study, findings do have some important clinical implications. Given that boys with FXS-ASD showed more pragmatic language impairment than boys with FXS-O, performing comparably to boys with idiopathic autism on a direct-assessment measure, the diagnosis of ASD in boys with FXS should be considered during assessment and clinicians may consider interventions that have been studied in the context of ASD when tailoring intervention approaches for boys with FXS-ASD. Our divergent findings depending on assessment method also support the use of multiple assessments, including natural language samples, to fully characterize pragmatic language ability and identify specific targets for intervention which may differ across groups and individuals.

The group similarities in directly assessed pragmatic language ability and theory of mind in ASD-O and FXS-ASD may have important implications for furthering knowledge of the brain and gene basis of these complex skills. In particular, because much is known about the molecular and neurobiological basis of FXS, the considerable overlap observed with ASD-O may help to define specific phenotypes associated with known genetic variation, in this case variation in the *FMR1*. We observed correlations with molecular genetic variables that support this association – pragmatic language on the CASL and theory of mind were both associated with *FMR1*-related variation in the FXS group. Specifically, greater methylation was associated with lower theory of mind performance and more impaired pragmatic language ability. Higher CGG repeat numbers were also related to poorer pragmatic language skills. Genetic variables showed additional associations with general cognition and structural language, which is perhaps not surprising given that general cognitive and language functioning certainly contribute to pragmatic language and theory of mind abilities. By providing a link between genetic and phenotypic variation, these findings may offer a foothold for understanding gene-behavior relationships in atypical and typical development alike.

This study has some limitations. First, we determined autism status primarily with the ADOS, but future studies should utilize information from both the ADOS and ADI-R for all participants to confirm autism status. Second, we did not examine all potential underlying mechanisms of social communication, such as anxiety or various aspects of executive function. Third, we examined social communication and theory of mind at one time point and in boys only. Future studies should assess these skills longitudinally and in both boys and girls.

In sum, this study identified pragmatic language and theory of mind as important abilities that are impaired in autism, and in a subgroup of children with FXS who also meet criteria for autism. This considerable phenotypic overlap between autism and a known monogenic condition suggests that impairments in pragmatic language ability and theory of mind may be tied to a particular genetic variant – the *FMR1*. Further studies are needed to clarify those particular types of pragmatic language difficulties common to both conditions, given that results from the pragmatic language subscales on the informant-based CCC-2 were not as straightforward as those obtained from direct-assessment of pragmatic language ability, or theory of mind for that matter. An additional important area for further study concerns the brain basis of these abilities, and the extent to which impairments may stem from similar neural architectural differences. By integrating detailed phenotypic analysis with neuroimaging studies in autism and FXS, future research may provide important insights into the role of *FMR1* in social-communicative phenotypes.

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APPENDIX

Task	Materials/set-up	Script	Control/test questions
Perspective taking[a]	Clear picture frame with blue fish on one side, white fish on the other. Examiner sits across from participant	"We are going to look at a picture of a fish. What color is the fish? Okay let's switch spots. (*Examiner switches seats with participant, without moving orientation of frame*). Now what color is the fish?"	Control: none Test: "What color fish do I see over here?
Diverse desires[b]	Picture of a broccoli and cookie; female adult figurine	"Here's Grandma. It's snack-time. Grandma wants a snack to eat. Here are two snacks, broccoli and a cookie. Which do you like best? Well that's a good choice, but Grandma really likes [opposite]. She doesn't like [participant's choice]. What she likes best is [opposite]"	Control: none Test: "Now it's time to eat. Grandma can only choose one snack, just one. Which snack will Grandma choose?"
Diverse belief[b]	Girl figurine, displayed midway between a picture of a bush and a garage	"Here's Amy. She wants to find her cat. Her cat might be hiding in the bushes or it might be hiding in the garage. Where do you think the cat is? Well, that's a good idea but Amy thinks her cat is in the [opposite]"	Control: none Test: "Where will Amy look for her cat?"
False belief[b]	Goldfish crackers box with plastic toy dog inside; boy figurine	"Here's a Goldfish box, what do you think is inside the Goldfish box? Let's see. It's really a dog inside! Okay, what is in the box?" "Here comes Sam. Sam has never looked inside this Goldfish box"	Control: "Did Sam look inside this box?" Test: "What does Sam think is in the box?"
Knowledge access[b]	Box with a ball inside; girl figurine	"Here's a box. What do you think is inside the box? Let's see... It's really a ball inside! So, what is in the box? Here's Amy. She's never looked inside this box"	Control: "Did Amy look inside this box?" Test: "Does Amy know what is in the box?
Explicit false belief[b]	Picture of a backpack and closet; boy figurine	"Here's Sam. Sam really wants to find his game. Sam's game may be in his backpack. Or it may be in the closet. Well, really Sam's game is in his backpack. But Sam thinks his game is in the closet"	Control: "Where is Sam's game really?" Test: "Where will Sam look for his game?"
Unexpected contents false belief[c,d]	Cardboard M and M's box filled with buttons. Second examiner, who has left the room	"What do you think is in this box? Lets' look inside and see. What's in here?"	Control: "When I first showed you the box, what did you think was inside it before you opened it?" Test: "[Second examiner] has never seen what is in this box. What will she think is in the box?"
Unexpected transfer false belief[c,d]	A pen. Second examiner places the pen on the table and announces "I need to go find my bag in the other room- I'll leave my pen right here where it is safe"	"I know, let's play a trick on [second examiner]. Let's hide her pen. Where do you want to hide it?"	Control: "Where is the pen really?" Test: "When [second examiner] comes back, where will she look for her pen?"
Simple desires[e]	Bowl of Goldfish crackers and bowl of rice cakes	"It's snack-time! Which do you like better? (*Examiner tastes each food*). Mmm [opposite of child's preferred snack]! Mmm, I tasted the [opposite]! Mmm! Eww [child's choice]! Eww, I tasted [child's choice]. Eww!"	Control: none Test: "Can you give me some?" (*Examiner holds out hand*)
Appearance-reality[f]	Sponge that looks like a rock; Candle that is shaped like a crayon; Doll that is covered with a ghost cloth; White card covered by translucent pink cellophane	"When you look at this, what does it look like?	Control: none Test: "What is it really? But what does it look like?"

[a] *Slaughter et al. (2007);* [b] *Wellman and Liu (2004);* [c] *Matthews et al. (2003);* [d] *Lewis and Mitchell (1994);* [e] *Repacholi and Gopnik (1997);* [f] *Flavell et al. (1983).*

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Pragmatic abilities of children with Williams syndrome: a longitudinal examination

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Prior research has indicated that pragmatics is an area of particular weakness for individuals with Williams syndrome (WS). To further address this aspect of the WS social phenotype, we used an individual differences approach to consider both cross-sectional and longitudinal relations among different pragmatic abilities for 14 children with WS, taking into account individual differences in non-verbal reasoning abilities. We also considered the relations between pragmatic abilities and expressive vocabulary ability. Participants were tested at two time points: as 4-year-olds during a 30-min play session with their mothers (Time 1) and an average of 5.87 years later during a one-on-one conversation with a familiar researcher (Time 2). Children's intellectual and expressive vocabulary abilities were assessed at both time points. Results indicated that the ability to verbally contribute information beyond what was required in response to a question (ExtendQ) was significantly related to the ability to verbally contribute new information in the absence of a question (ExtendS) both at age 4 years and during primary school. At age 4, both the ability to pair verbalizations with eye contact in triadic interactions (secondary intersubjectivity) and expressive vocabulary ability were related to both ExtendQ and ExtendS. Finally, both ExtendQ and the ability to pair verbalizations with eye contact (intersubjectivity) at age 4 years predicted ExtendQ at age 9–12 years. The theoretical implications of our findings and the importance of early pragmatic language intervention for children who have WS are discussed.

Keywords: Williams–Beuren syndrome, conversation, social communication, pragmatics, longitudinal, intellectual disability

INTRODUCTION

Williams syndrome (WS) is a complex neurodevelopmental disorder resulting from a hemideletion of 26 genes on chromosome 7q11.23 (Hillier et al., 2003). The prevalence of WS is estimated to be 1 in 7500 live births (Strømme et al., 2002) with both genders equally likely to be affected (American Academy of Pediatrics Committee on Genetics, 2001). Like most genetic syndromes, WS is associated with a specific physical and medical phenotype which includes dysmorphic facial features, heart disease (most commonly supravalvar aortic stenosis), connective tissue abnormalities, failure to thrive, and growth deficiency (Morris, 2006). The majority of children with WS demonstrate developmental delay that typically leads to mild to moderate intellectual disability or learning difficulties, although some individuals have low average to average intelligence. In addition, WS is associated with a specific cognitive profile characterized by relative strengths in verbal short-term memory and the structural and concrete vocabulary components of language accompanied by considerable weakness in visuospatial construction (Udwin and Yule, 1991; Mervis et al., 2000; Mervis and Morris, 2007).

Williams syndrome has drawn considerable attention from researchers and the general public due to the unique behavioral profile associated with this disorder. Individuals with WS demonstrate a considerable amount of interest in others (Klein-Tasman and Mervis, 2003; Mervis et al., 2003; Klein-Tasman et al., 2011) and are often described as outgoing and talkative and never going unnoticed in a group (Dilts et al., 1990; Fryns et al., 1991; Gosch and Pankau, 1997; Dykens and Rosner, 1999). These behavioral characteristics are likely a significant contributor to some authors' characterization of the WS social phenotype as the opposite of the autism social phenotype (e.g., Cowley, 2003; Levy et al., 2011). However, despite their sociable nature, individuals with WS have considerable difficulty navigating the surrounding world of people. Children with WS are delayed in the development of the ability to understand another person's perspective or theory of mind, an impairment that is also characteristic of the autism social phenotype (Tager-Flusberg et al., 1997; Tager-Flusberg and Sullivan, 2000; John and Mervis, 2009). In addition, individuals with WS have difficulty establishing and maintaining peer relationships (e.g., Davies et al., 1998; Sullivan et al., 2003) and most adults are socially isolated and do not typically engage in social interactions with peers (Udwin, 1990).

Difficulties with socio-communicative abilities likely contribute to these problems. To date, there have been no published studies of individuals with WS examining the stability of individual differences for the same type of pragmatic ability across time, and the only published study that addressed relations between pragmatic abilities and vocabulary abilities in individuals with WS (John et al., 2009) was cross-sectional and focused on receptive vocabulary rather than expressive. In the present study, to further

understand the WS social phenotype, we considered whether individual differences in verbally contributing new information within a social interaction were related to the child's rate of pairing verbalizations with eye contact in triadic interactions and/or the child's expressive vocabulary ability, beyond the levels expected as a function of the children's non-verbal intellectual abilities. Children participated in this study twice, once as preschoolers and once approximately 6 years later, during primary school. Thus, we also were able to examine the relative stability of individual differences in children's verbal contribution of new information to a social interaction during the preschool and primary school-age periods and whether pairing verbalizations with eye contact and/or expressive vocabulary ability at age 4 years predicted the ability to verbally contribute new information during the primary school years beyond what would be expected given the children's non-verbal intellectual abilities.

SOCIO-COMMUNICATIVE AND PRAGMATIC LANGUAGE ABILITIES OF INDIVIDUALS WITH WILLIAMS SYNDROME

Over the last decade, a considerable amount of research has been dedicated toward understanding the intricacies of social cognitive and pragmatic development in individuals with WS. This body of literature stemmed from researchers' desire to understand why, despite their sociable nature and relative strength in the concrete and structural aspects of language, individuals with WS experienced so much difficulty establishing and maintaining peer relationships. The findings from these studies indicate that pragmatic difficulties are present across the life span.

Early in development, children with WS demonstrate delay in the emergence of joint attention ability – the ability to coordinate one's attention between a person and an object or event of mutual interest – not only relative to chronological age (CA) but also relative to language ability (Mervis and Bertrand, 1993, 1997; Mervis et al., 2003). In addition, young children with WS are significantly less likely to engage in triadic joint attention than are either mental-age matched typically developing (TD) children (Laing et al., 2002) or children with Down syndrome (DS) matched on CA, developmental quotient (DQ), and expressive vocabulary size (Rowe et al., 2005). Findings from two studies focused on the performance of toddlers and preschoolers with WS on a semi-structured play-based assessment (Autism Diagnostic Observation Schedule-Generic, Module 1; Lord et al., 1999) indicated that approximately half of the participants in each study did not clearly integrate eye contact to reference an out-of-reach object to their communicative partner and the majority of participants did not integrate eye contact or vocalizations with acts of showing objects (Klein-Tasman et al., 2007; Lincoln et al., 2007). Finally, despite having significantly higher DQs, preschoolers with WS have significantly more difficulty inferring the communicative intent behind pointing and eye gaze gestures than do CA-matched preschoolers with DS (John and Mervis, 2010).

The development of joint attention has been argued to demonstrate the child's recognition of people as intentional agents (e.g., Tomasello, 1995; Thompson, 2006). Furthermore, for TD children, early triadic joint attention ability has been shown to predict later language development and the development of the ability to understand another person's perspective or theory of mind (e.g., Tomasello, 1995; Baldwin and Moses, 1996; Charman et al., 2000, 2003). As discussed by John et al. (2009), successful communication is partially dependent on the ability to take another person's perspective. Given the relation between early triadic joint attention abilities and later theory of mind in typical development, it is likely that the early impairments in triadic joint attention evidenced by children with WS are a contributing factor to their later impairments in pragmatics. While this hypothesis has not been tested directly, empirical findings documenting pragmatic difficulties during the adolescent and adult years and the significant association between pragmatic language ability and theory of mind for individuals with WS (e.g., Jones et al., 2000; Laws and Bishop, 2004; John and Mervis, 2009) are consistent with this hypothesis.

Several research groups have addressed the general pragmatic abilities of individuals with WS beyond the preschool years using parental responses on the Children's Communication Checklist (CCC; Bishop, 1998) or the CCC-2 (Bishop, 2002). Results have indicated that individuals with WS demonstrate particular difficulty with the use of stereotyped phrases, inappropriate initiation of conversations, and overdependence on context to interpret what was said to them (Laws and Bishop, 2004; Peregrine et al., 2005; Philofsky et al., 2007; Harmon et al., 2009). Some of these difficulties are comparable to those evidenced by children with autism; Philofsky et al. (2007) reported that school-age children with WS and CA-matched children with autism evidenced similar levels of impairment on the Inappropriate Initiation and Use of Context scales of the CCC-2. Klein-Tasman et al. (2011) administered the Social Responsiveness Scale (SRS; Constantino and Gruber, 2005) to the parents of eighty-two 4- to 16-year-olds with WS and to the teachers of 49 of the children. Although the mean *T* score on the Social Motivation subscale was in the average range for TD children based on both parental and teacher report, mean *T* scores were in the mild to severe difficulty range for the remaining subscales (Social Awareness, Social Cognition, Social Communication, and Autistic Mannerisms), indicating considerable difficulty with many components of reciprocal social reciprocity.

In addition, several researchers have directly examined the conversational abilities of individuals with WS. Udwin and Yule (1990) collected 30 min conversations with a researcher for 43 children with WS (mean CA = 11.1 years). The authors found that 37% of the participants met their criteria for hyper-verbal speech (fluent speech including an excessive number of stereotyped phrases or idioms, over-familiarity, introduction of irrelevant personal experiences, and perseverative responding). More recently, Jones et al. (2000) examined the spontaneous use of social language during a Biographical Interview task, which involved asking each participant questions about his or her family, activities, and interests. The authors reported data for adolescents and adults with WS ($n = 10$; mean CA = 15.8 years), CA- and IQ-matched individuals with DS ($n = 10$; mean CA = 15.1 years), and TD children matched on mental-age ($n = 8$; mean CA = 6.5 years). The number of interview questions answered by the three groups did not differ statistically. However, the WS group used significantly more evaluative devices (descriptions of affective states, evaluative comments, empathic markers, and character speech) than did either comparison group. Jones et al. also noted that the participants

with WS often asked the interviewer personal questions and perseverated even when the interviewer tried to redirect them.

Stojanovik (2006) compared the pragmatic language abilities of five children with WS (mean CA = 9.17 years) to those of eight children with specific language impairment (SLI) matched for receptive vocabulary and grammatical ability (mean CA = 10.58 years) and nine TD children (mean CA = 8.67 years) during a semi-structured conversation. The children with WS were significantly less likely than were the children in either comparison group to add information to the conversation beyond that explicitly requested by their conversational partner. In addition, regardless of whether the researcher asked for information or clarification, the responses of the children with WS were less likely to be adequate than were the responses of either the children with SLI or the TD children. More specifically, the WS group was more likely to provide too little information or to misinterpret what the researcher had meant.

Finally, John et al. (2009) used a barrier listener-role referential communication task to examine the ability of children with WS ($n = 57$; mean CA = 9.24 years) to verbalize message inadequacy. In this task, a researcher instructed the children to place a smaller picture on a larger scene. Although the children performed well when the researcher's instructions were adequate, they had considerable difficulty when the researcher provided inadequate instructions (i.e., the requested picture was not available, the instruction was ambiguous, or the instruction contained vocabulary that the child did not understand). Children verbally indicated that a problem was encountered less than half of the time on average and most of their verbalizations were either too vague for the researcher to determine the nature of the problem or indicated the wrong problem. Children's ability to verbalize message inadequacy was related to CA and theory of mind ability.

Given the findings of the studies examining the conversational abilities of individuals with WS conducted to date, it is not surprising that the WS social phenotype includes difficulties establishing and maintaining friendships. Even though individuals with WS demonstrate a sociable nature and are interested in interacting with others, tendencies to use stereotyped and perseverative utterances, to provide too little information or to misinterpret what their communicative partner meant, and to be less likely to contribute new information to the interaction likely serve as serious roadblocks in social interactions with peers.

While progress has been made in describing the pragmatic language abilities of individuals with WS across the lifespan, much remains to be understood. For example, to date there have been no studies reported that examined the stability of individual differences in the pragmatic language abilities of people with WS across time. In addition, although Fidler et al. (2007) have hypothesized that early difficulties with secondary intersubjectivity (relating/connecting to other people in triadic interactions) play a key role in the development of the WS phenotype, the question of whether secondary intersubjectivity ability is related to concurrent pragmatic language abilities or predicts later pragmatic language abilities in individuals with WS has not been addressed empirically. The purpose of the present study was to begin to address these gaps in the literature. The same types of pragmatic language data and expressive vocabulary ability data were collected on a group of children with WS at two time points. At Time 1, when the children were 4 years old, providing new information to a verbal interaction beyond what was explicitly requested (both in response to a question and in the absence of a question) was assessed during a 30-min play session with their mothers. An average of 5.87 years later (Time 2), the same pragmatic variables were assessed during a 7-min one-on-one conversation with a familiar researcher. Expressive vocabulary and non-verbal intellectual ability were assessed at both time points using standardized measures. Finally, the pairing of verbalizations with eye contact during the play session at Time 1 (a measure of secondary intersubjectivity) was also assessed.

We addressed several research questions. Our first set of questions was cross-sectional and was considered separately for Time 1 (preschool) and Time 2 (primary school). In particular, we sought to determine if there were significant relations among individual differences in the rates of the two pragmatic language measures (frequency of occurrence per minute) for children with WS: (1) extending a verbal interaction in response to a question and (2) extending a verbal interaction when a question had not been asked, after controlling for individual differences in non-verbal intellectual ability. We also addressed the question of whether the rates of these pragmatic behaviors were related to rate of pairing verbalizations with eye contact (secondary intersubjectivity) and/or expressive vocabulary ability, even after controlling for individual differences in non-verbal intellectual ability.

Our second set of questions was longitudinal. In particular, we sought to determine if individual differences in the pragmatic language abilities we measured were stable from the preschool period to the primary school period, after controlling for individual differences in non-verbal intellectual ability. We also considered the question of whether rate of pairing verbalizations with eye contact (secondary intersubjectivity) at age 4 years and/or expressive vocabulary ability at age 4 years (Time 1) predicted rate of extending a verbal interaction either in response to a question or in the absence of a question approximately 6 years later (Time 2) even after differences in non-verbal intellectual ability had been taken into account.

MATERIALS AND METHODS

PARTICIPANTS

Participants were 14 children with genetically confirmed classic-length WS deletions (7 boys, 7 girls) for whom data were available at two time points. At Time 1, mean CA was 4.30 years (SD = 0.25, range: 4.01–4.65). The children were re-assessed an average of 5.87 years later (SD = 1.04, range: 4.48–7.60). The children's mean CA at Time 2 was 10.18 years (SD = 1.08, range: 9.02–12.06). The racial/ethnic constitution of the sample was 7% White Hispanic and 93% White Non-Hispanic.

MEASURES

Differential Ability Scales

The Differential Ability Scales (DAS) is an individually administered standardized measure of verbal, non-verbal reasoning, and spatial (visuospatial construction) abilities that yields a General Conceptual Ability (GCA; similar to IQ) standard score (SS) and several cluster SSs. The mean for the general population is 100

with a SD of 15 for both the GCA and the cluster SSs. Participants completed the DAS-Preschool Version (DAS; Elliott, 1990) at Time 1 and the DAS-II School-Age Version (DAS-II; Elliott, 2007) at Time 2. Non-verbal intellectual ability was measured by the DAS-Preschool Nonverbal cluster SS at Time 1; the subtests included in this cluster measure non-verbal reasoning and visuospatial construction. Non-verbal intellectual ability at Time 2 was measured by the DAS-II Special Nonverbal Composite (SNC) SS, which is based on performance on the subtests included in the Nonverbal Reasoning and Spatial clusters.

Expressive Vocabulary Test

The Expressive Vocabulary Test (EVT) is an individually administered standardized measure of expressive vocabulary ability. The mean for the general population is 100 with a SD of 15. Participants completed the EVT (Williams, 1997) at Time 1 and the EVT-2 (Williams, 2007) at Time 2.

Pragmatic Language Samples

The children's language during two spontaneous interactions with an adult, one at each time point, was transcribed and coded. At Time 1, each child participated in a 30-min play session with his or her mother in a laboratory playroom equipped with developmentally appropriate toys. At Time 2, each child participated in a 7-min conversation with a familiar researcher who was instructed to attempt to maintain a conversation with the child for the entire 7 min period. The researcher was given a list of suggested topics to introduce if she was unable to maintain the conversation by following the child's lead. The videotapes of the Pragmatic Language Samples were transcribed by trained research assistants and marked to indicate the presence of any pauses lasting 3 s or longer. Two research assistants checked the original transcript against the original video recording and made any changes necessary to arrive at a consensus transcript.

PROCEDURE

At both time points, children completed a battery of cognitive and language assessments including an assessment of intellectual abilities (DAS) and an assessment of expressive vocabulary (EVT). These measures were administered according to the test authors' instructions and were usually completed within a day of the measure of pragmatic language ability (Play session at Time 1 and Conversation at Time 2). The Pragmatic Language Samples were coded using the procedure described in the next section.

TRANSCRIPT CODING

Children's verbalizations during the Pragmatic Language Samples at both time points were coded for two pragmatic language variables: ExtendS (statements that the child made – not in response to adult questions – that served to appropriately extend the conversation) and ExtendQ (statements or questions that the child produced – in response to adult questions – that served to appropriately extend the conversation). In addition, children's EyeContact (utterances produced by the child that were accompanied by eye contact with the conversational partner) was coded at Time 1 as a measure of early secondary intersubjectivity. The coding system for each of these variables is described below.

ExtendS

Each statement that (1) the child produced in response to a statement made by the adult, (2) the child provided following a pause of more than 3 s, or (3) if the child already held the floor, extended the conversation by adding new information was coded "yes" or "no." Children's statements were coded "yes" if they added new information to the interaction and did not fit either of the categories below. Statements were coded "no" if they did not add new information or they fit either of the following categories:

1. The child's response pertained to an inappropriate topic (e.g., personal bodily functions).
2. The child's statement insulted either the adult or a third party.

For each child at each time point, the variable ExtendS represented the rate per minute of statements (not made in response to a question) produced by the child that were coded "yes." This variable was calculated by dividing the number of statements (not made in response to a question) produced by the child that were coded "yes" by the length of the Pragmatic Language Sample (in minutes). High agreement was observed for both Time 1 (percentage of agreement = 92%, $\kappa = 0.83$) and Time 2 (percentage of agreement = 91%, $\kappa = 0.78$).

ExtendQ

Each verbal response to an adult question that the child produced was coded "yes" or "no." Responses were coded "yes" if they either added appropriate information to the interaction beyond what was directly requested or if they both responded to the adult's question and included as part of their response an appropriate question directed toward the adult. Responses to questions were coded "no" if they fit any of the following categories:

1. The child's response pertained to an inappropriate topic (e.g., personal bodily functions).
2. The child's response insulted either the adult or a third party.
3. The child did not answer the adult's question within 4 s.
4. The child ignored the question asked by the adult and produced an unrelated utterance.
5. The child's response included a question which he or she had previously asked multiple times and to which the adult had responded at least three times. The child's response was coded "yes" the first three times he or she asked a particular question and the adult answered the question. If the child continued to ask the same question even after the adult answered the question three times, subsequent repetitions of the question were coded "no." For example, if the child asked the same question five times (and the adult answered all five times), the first three times were coded "yes" and the last two were coded "no."

For each child at each time point, the variable ExtendQ represented the rate per minute of the child's responses to adult questions that were coded "yes." This variable was calculated by dividing the number of the child's responses to adult questions that were coded "yes" by the length of the Pragmatic Language Sample (in minutes). High agreement was observed for ExtendQ at both Time 1 (percentage of agreement = 98%, $\kappa = 0.74$) and Time 2 (percentage of agreement = 95%, $\kappa = 0.69$).

EyeContact

At Time 1, each utterance produced by the child was coded "yes" or "no." Children's utterances were coded "yes" if the child made eye contact with the adult at any point during the verbalization and the utterance did not fit in either of the categories below. Utterances were coded "no" if the child did not make eye contact with the adult at any point during the utterance or if the utterance fit in either of the following categories:

1. The child's utterance only included a sound effect (e.g., eating or drinking noises, animal sounds).
2. The child's utterance was completely unintelligible.

For each child at each time point, the variable EyeContact represented the rate per minute of utterances produced by the child that were coded "yes." This variable was calculated by dividing the number of utterances produced by the child that were coded "yes" by the length of the Pragmatic Language Sample (in minutes). High agreement was observed for EyeContact at Time 1 (percentage of agreement = 95%, $\kappa = 0.98$). This variable could not be coded at Time 2, since the Pragmatic Language Sample at Time 2 was a dyadic interaction instead of a triadic interaction.

RESULTS

PRAGMATIC ABILITY AT TIME 1

Descriptive statistics for performance on the standardized assessments at Time 1 are reported in **Table 1**. Relative to prior reports of SSs for children with WS on these measures (e.g., Mervis and Morris, 2007), the mean level of performance of the present group of children was higher. The variability among children was at or above the typical level.

Descriptive statistics for the variables computed from the Pragmatic Language Sample at Time 1 are reported in **Table 2**. As both the assessment SSs and the variables from the Time 1 Pragmatic Language Sample met the necessary statistical assumptions for use of parametric analyses, Pearson correlations were used to compute relations among the dependent variables. Bivariate correlations of non-verbal intellectual ability with the pragmatic language variables, the secondary intersubjectivity variable, and expressive vocabulary ability at Time 1 are shown in **Table 3** ($\alpha_{fw} = 0.0125$). As *a priori* positive relations were predicted for all analyses conducted as part of this project, one-tailed tests were used throughout. As indicated in **Table 3**, non-verbal intellectual ability was significantly and strongly related to expressive vocabulary ability and marginally related to ExtendS. To control for individual differences in non-verbal intellectual ability, we computed partial correlations for the remaining Time 1 analyses, controlling for DAS Nonverbal cluster SS. The first set of partial correlations examined relations among EyeContact, ExtendS, and ExtendQ at Time 1 ($\alpha_{fw} = 0.025$). At Time 1, EyeContact was significantly related both to ExtendS ($r = 0.63$, $p = 0.01$) and to ExtendQ ($r = 0.68$, $p = 0.008$) even after the effects of non-verbal intellectual ability were controlled. The correlation between ExtendS and ExtendQ was also significant ($r = 0.80$, $p = 0.001$) even after controlling for non-verbal intellectual ability. Partial correlations were also computed to determine the relation between the two pragmatic language variables (ExtendS and ExtendQ) and expressive vocabulary ability (EVT SS). Results indicated that even after controlling for non-verbal intellectual ability, both ExtendS ($r = 0.52$, $p = 0.04$) and ExtendQ ($r = 0.53$, $p = 0.04$) were significantly correlated with EVT SS.

PRAGMATIC ABILITY AT TIME 2

Descriptive statistics for performance on the standardized assessments at Time 2 are also reported in **Table 1**. The children's SSs were slightly higher than previously reported for children with WS (e.g., Mervis and John, 2010) but evidenced the expected amount of variability.

Table 1 | Descriptive statistics for standardized assessment performance (standard scores) as a function of time point.

Measure	Time 1			Time 2		
	M	SD	Range	*M*	SD	Range
DAS GCA	72.69	15.88	44–92	67.36	13.00	43–91
DAS Nonverbal/SNC	69.77	15.95	43–92	63.07	13.05	41–86
EVT SS	91.57	21.86	40–116	85.79	16.03	58–112

Time 1 assessments: DAS GCA, DAS Nonverbal cluster, EVT. Time 2 assessments: DAS-II GCA, DAS-II Special Nonverbal Composite (SNC), EVT-2.

Table 2 | Descriptive statistics for rates of Pragmatic Language Sample variables as a function of time point.

Coded behavior	Time 1			Time 2		
Measure	*M*	SD	Range	*M*	SD	Range
SUCCESS RATE (NUMBER OF YES CODES PER MINUTE)						
EyeContact	1.59	1.06	0–3.80	–	–	–
ExtendS	1.47	0.84	0–3.20	1.00	0.81	0–3.14
ExtendQ	0.32	0.26	0–0.90	0.59	0.48	0–1.57
FAILURE RATE (NUMBER OF NO CODES PER MINUTE)						
EyeContact	6.23	3.11	0.10–12.33	–	–	–
ExtendS	1.61	0.75	0–3.00	1.20	0.61	0–2.00
ExtendQ	3.23	0.96	1.70–5.03	6.44	1.77	3.43–8.86

Table 3 | Bivariate correlations of non-verbal intellectual ability with pragmatic language variables, secondary intersubjectivity, and expressive vocabulary ability as a function of time point.

Measure	Time 1	Time 2
EyeContact	0.13	–
ExtendS	0.52*	0.53*
ExtendQ	0.40	0.25
EVT	0.86***	0.76***

*Time 1: Non-verbal intellectual ability: DAS Nonverbal cluster SS, Expressive vocabulary ability: EVT SS. Time 2: Non-verbal intellectual ability: DAS-II SNC, Expressive vocabulary ability: EVT-2 SS. *$p \leq 0.05$, ***$p \leq 0.001$.*

Descriptive statistics for performance on the variables computed from the Time 2 Pragmatic Language Sample are reported in **Table 2**. Data from the Time 2 standardized assessments and the pragmatic language variable ExtendQ met the necessary statistical assumptions for use of parametric analyses. As the distribution for ExtendS violated the parametric assumption of normality, a logarithmic transformation was applied. Bivariate correlations of non-verbal intellectual ability with the pragmatic language variables and expressive vocabulary ability at Time 2 also are shown in **Table 3** ($\alpha_{fw} = 0.0125$). Non-verbal intellectual ability was significantly and strongly related to expressive vocabulary ability and marginally related to ExtendS. To control for individual differences in non-verbal intellectual ability, we computed partial correlations for the remaining Time 2 analyses, controlling for DAS-II SNC. There was a significant correlation between logExtendS and ExtendQ ($r = 0.59$, $p = 0.02$) after controlling for the effects of non-verbal intellectual ability. Partial correlations were also computed to determine the relation between the two pragmatic language variables and expressive vocabulary ability (EVT-2 SS) at Time 2 after controlling for the effects of non-verbal intellectual ability. Neither correlation was significant (logExtendS: $r = 0.29$; ExtendQ: $r = 0.19$).

RELATIONS ACROSS TIME 1 AND TIME 2

To examine the stability of individual differences in pragmatic language ability across the two time points after controlling for non-verbal intellectual ability at both time points, one-tailed Pearson correlation coefficients were computed controlling for both DAS Nonverbal SS and DAS-II School-Age SNC. Results indicated that Time 1 ExtendQ was significantly correlated with Time 2 ExtendQ ($r = 0.64$, $p = 0.02$). The correlation between ExtendS at Time 1 and Time 2 ($r = 0.26$, $p = 0.23$) was not significant. One-tailed partial correlation coefficients were also computed to determine if Time 1 EyeContact predicted Time 2 logExtendS or Time 2 ExtendQ. Results indicated that after controlling for non-verbal intellectual ability at both time points, Time 1 EyeContact predicted Time 2 ExtendQ ($r = 0.72$, $p = 0.01$) but did not predict Time 2 logExtendS ($r = 0.23$, $p = 0.26$). Finally, one-tailed Pearson correlation coefficients were also computed controlling for non-verbal intellectual ability at both Time 1 and Time 2 to determine if expressive vocabulary ability (EVT SS) at Time 1 predicted Time 2 logExtendS or Time 2 ExtendQ. Neither correlation was significant (ExtendQ: $r = 0.15$, $p = 0.31$, logExtendS: $r = -0.18$, $p = 0.34$).

DISCUSSION

Considerable attention has been drawn to the WS social phenotype due to its seemingly paradoxical nature. Although children with WS are described as highly gregarious and friendly, they have considerable difficulty establishing and maintaining friendships (e.g., Dilts et al., 1990; Gosch and Pankau, 1997; Dykens and Rosner, 1999; Sullivan et al., 2003). Similarly, even though children with WS demonstrate relative strengths in the structural aspects of language and in concrete vocabulary, they typically have difficulties with the pragmatic aspects of language (see Mervis and Becerra, 2007; Mervis and John, 2010 for review). These findings from prior research serve as a reminder that successful navigation of the social world requires more than just an interest in interacting with others, a relatively good vocabulary, and the ability to produce grammatical sentences; it also depends on a complex interweaving of cognitive, affective, and personality factors. In the present study, we sought to contribute to the growing literature exploring the WS social phenotype by examining the relations (beyond those accounted for by non-verbal intellectual ability) between individual differences in the following abilities both concurrently and predictively: verbal extension of an ongoing social exchange by contributing new information (both in response to questions and in the absence of questions) and expressive vocabulary. In addition, we examined whether or not individual differences in the coordination of eye contact and a verbal utterance (secondary intersubjectivity) predicted pragmatic language ability an average of 6 years later. In the remainder of the Discussion, we first address our cross-sectional findings separately as a function of time point and then consider our longitudinal findings. We then focus on the implications of these findings, the limitations of the present study, and future directions.

CONCURRENT RELATIONS

At both Time 1 (age 4 years) and Time 2 (age 9–12 years), the ability to verbally contribute new information beyond that requested in response to a question was significantly related to the ability to verbally contribute new information in the absence of a question, even after the effects of non-verbal intellectual ability were controlled. Furthermore, at Time 1, expressive vocabulary ability was significantly positively correlated with individual differences in children's ability to contribute new information both in response to questions and in the absence of questions even after controlling for the effects of non-verbal intellectual ability. The positive relation between expressive vocabulary ability and rate of extending a conversation either in response to a question or in the absence of a question at Time 1, even after controlling for individual differences in non-verbal intellectual ability, may reflect the fact that at age 4 years, the vocabularies of many of the children were limited, making providing information beyond what was requested challenging. The partial correlations between expressive vocabulary ability and contributing new information to the conversation beyond what was requested were not significant at Time 2. This difference from Time 1 may have been due to the fact that by school age the vocabularies of all of the children were adequate for contributing information beyond what was requested to an interaction.

At age 4 years, there also was a clear positive association between the rate of pairing verbalizations with eye contact (secondary intersubjectivity) and the rate of verbally adding information to a social interaction beyond what was required, both in response to a question and in the absence of a question, even after controlling for the effects of non-verbal intellectual ability. Although this study was the first to specifically examine the relation between use of eye contact when talking with another person (intersubjectivity) and pragmatic language ability in children with WS, many researchers have addressed the role of eye contact within social interactions involving TD children (e.g., Argyle and Cook, 1976). The content of a communicative interaction is comprised of more than just the words that are exchanged between partners; the surrounding

context; and non-verbal behaviors exchanged between partners also significantly contribute to the content (Clark and Marshall, 1981; Clark, 1996; Richardson et al., 2009). Eye contact serves as a way of accessing this additional information. Pairing eye contact with a communicative act in triadic interactions has been described as secondary intersubjectivity, a demonstration of an awareness of shared mental states (e.g., Zlatev, 2008). It has been theorized that early deficits in secondary intersubjectivity negatively affect later communicative competence. For example, in the case of individuals who have autism spectrum disorders, early deficits are observed in many behaviors reflecting secondary intersubjectivity such as joint attention and intentionality (American Psychiatric Association, 2000); these early deficits have been hypothesized to lead to the later difficulties in pragmatic language that are observed in individuals who have autism spectrum disorders (Rogers, 1998). The associations we found between pairing utterances with eye contact to the communicative partner during play with toys (secondary intersubjectivity) and verbally providing new information within a social exchange (pragmatics) is consistent with the argument that intersubjectivity is related to pragmatic ability.

We were unable to examine the relation between secondary intersubjectivity and verbal provision of information beyond what was requested at age 9–12 years due to context differences between our Time 1 and Time 2 Pragmatic Language Samples. In particular, because the Time 2 Pragmatic Language Sample involved a dyadic interaction rather than a triadic interaction, coding the rate that children paired verbalizations with eye contact would result in a measure of primary intersubjectivity (relating/connecting to other people in dyadic interactions). Children with WS have been shown to use eye contact during dyadic interactions at similar levels or higher levels as mental-age matched TD children (Laing et al., 2002). In contrast, in triadic joint attention situations, children with WS use eye contact significantly less often than either mental-age matched TD children (Laing et al., 2002) or children with DS matched for CA, DQ, and expressive vocabulary size (Rowe et al., 2005). Thus, primary and secondary intersubjectivity cannot be used interchangeably as measures of intersubjectivity for children with WS. It is important that future studies examine whether or not individual differences in secondary intersubjectivity remain stable across time for children with WS. Furthermore, given what is known about the dissociation between primary and secondary intersubjectivity in WS, longitudinal studies are needed that include both contexts that require triadic joint attention and contexts that require primarily dyadic joint attention. Such studies would be important for enhancing our understanding of the developmental trajectory of the use of eye contact by children with WS and its relation to pragmatic language.

Examination of the relations between pragmatic language ability across the two time points indicated that the rate of providing information beyond what was requested in response to a question at age 4 years significantly predicted the rate of providing information beyond what was expected in response to a question an average of 5.87 years later, even after controlling for non-verbal intellectual ability at both time points. Expressive vocabulary ability at age 4 did not predict school-age pragmatic ability. However, the rate of utterances children produced that were paired with eye contact (secondary intersubjectivity) as preschoolers did significantly predict the rate of provision of information beyond what was requested in response to questions during the school-age years, even after controlling for non-verbal intellectual ability at both time points.

Studies of joint attention in TD children have demonstrated that early joint attention ability predicts both later language development and the development of theory of mind (e.g., Tomasello, 1995; Baldwin and Moses, 1996; Charman et al., 2000, 2003). In addition to the role of language ability in conversational success, the ability to take the perspective of another person, or theory of mind, is vital for success in communicative interactions. John et al. (2009) found that the theory of mind ability of children with WS significantly and independently contributed to the likelihood that message inadequacy would be verbalized when the speaker's request was ambiguous. In addition, theory of mind ability significantly and independently contributed to the likelihood of effectively verbalizing the nature of the problem encountered when the speaker's message was ambiguous or when the speaker referred to the referent using a word that was not in the child's vocabulary. As triadic joint attention ability is a precursor to theory of mind and is a measure of secondary intersubjectivity, it is not surprising that we found that, for children with WS, early secondary intersubjectivity ability predicted later aspects of pragmatic language ability. This finding provides further support for the argument that early secondary intersubjectivity is a contributing factor to the development of pragmatic language ability.

IMPLICATIONS

The present study is the first to show a predictive association between early secondary intersubjectivity and later pragmatic ability in children with WS and to demonstrate consistency in individual differences in aspects of pragmatic language ability across time beyond what would have been expected given individual differences in non-verbal intellectual ability. The purpose of communicative exchanges often goes beyond just the transfer of information between individuals; communicative exchanges involve connecting with another person (Zlatev, 2008). Our longitudinal finding that early secondary intersubjectivity ability predicted later pragmatic language ability even after controlling for individual differences in non-verbal intellectual ability strongly suggests that limitations in secondary intersubjectivity early in development contribute to later deficits in pragmatic language, providing a causal link between two key components of the WS social phenotype. Thus, this longitudinal finding provides clear evidence of an important link between prior cross-sectional findings of impairments in aspects of secondary intersubjectivity (triadic joint attention) in very young children with WS (e.g., Klein-Tasman et al., 2007; Lincoln et al., 2007) and impairments in pragmatic language in older children with WS (e.g., Udwin and Yule, 1990; Laws and Bishop, 2004; Stojanovik, 2006; Philofsky et al., 2007).

In light of these predictive associations, it is important that interventions be developed targeting secondary intersubjectivity in young children with WS. Furthermore, as previously stressed by Mervis and Becerra (2007; see also Mervis and John, 2010; Mervis and Velleman, 2011), parents, therapists, and teachers need to be vigilant to avoid being deceived by the relatively good

expressive language of children with WS into assuming that their communicative skills are adequate for their developmental levels. Intervention programs such as the Early Start Denver Model (ESDM; Rogers and Dawson, 2010) that use a variety of techniques to directly address secondary intersubjectivity deficits provide a framework for targeting these skills in WS. Results of a randomized controlled trial of ESDM for children with autism spectrum disorders between 18 and 30 months of age indicated that 2 years after entering intervention children who received ESDM demonstrated significant improvements in IQ, adaptive behavior, and autism symptomology when compared to children who received intervention from community providers (Dawson et al., 2010). As discussed by Mervis and John (2010), the overlap in types of socio-communicative difficulties demonstrated by children with autism spectrum disorders and children with WS suggests that therapeutic approaches similar to ESDM will be appropriate and effective for children with WS, once modifications to account for differences in the behavioral phenotypes of children with WS as compared to children with autism spectrum disorders are made.

LIMITATIONS AND FUTURE DIRECTIONS

While the findings from the present study contribute to the growing literature exploring the WS social phenotype, we acknowledge some limitations. First, because the sample size was relatively small, we did not have adequate power to detect small to moderate effects. Second, because we did not include a contrast group, we were not able to address the question of whether the ability of children with WS to verbally contribute new information to a social interaction is similar to or different from that demonstrated by other groups with intellectual disability. We also were not able to address the generality of our longitudinal findings for children with other syndromes. The context in which the Time 1 Pragmatic Language Sample was collected (play with toys with the child's mother) differed from the context in which the Time 2 Pragmatic Language Sample was collected (conversation with a familiar adult, with no objects present), which may have reduced the extent of continuity of individual differences in pragmatic language abilities from age 4 years to age 9–12 years.

More research examining the longitudinal trajectories of primary and secondary intersubjectivity and pragmatic language and their relations to non-verbal ability and language ability for children with WS is needed, ideally with multiple data points across a wide age range. An important focus for this research would be to determine if individual differences in secondary intersubjectivity, which are strongly related to individual differences in pragmatic language abilities at age 4 years, are stable across time. In addition, it is important for future studies to examine the relations among primary intersubjectivity, secondary intersubjectivity, and pragmatic language ability over time. Finally, future studies (both cross-sectional and longitudinal) should also compare the pragmatic abilities of children with WS to those of matched children with other etiologies of intellectual disability to identify similarities and differences as a function of syndrome.

CONCLUSION

Over the past few decades, more and more interest has developed with regard to understanding the social phenotype associated with WS. Despite considerable interest in other people, children with WS demonstrate difficulty both with pragmatic language and with establishing and maintaining friendships. In the present study, we found that the ability to verbally contribute information beyond what was required in response to a question was significantly related to the ability to verbally contribute new information in the absence of a question during both the preschool years and the school-age years. During the preschool years, the ability to pair verbalizations with eye contact (secondary intersubjectivity) was related to the ability to verbally contribute information beyond the minimum expected within a social interaction. Finally, the ability to verbally contribute new information to a social interaction beyond what was required to answer a question and the ability to pair verbalizations with eye contact (secondary intersubjectivity) at age 4 years predicted the ability to verbally contribute new information beyond what was required to answer a question at age 9–12 years. Understanding the nature of the pragmatic abilities of children with WS over time and the relations of these abilities to social cognition, language ability, and non-verbal intellectual ability is a crucial step toward the development of interventions to address the socio-communicative difficulties evidenced by individuals with WS.

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Social cognition in Williams syndrome: relations between performance on the social attribution task and cognitive and behavioral characteristics

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Williams syndrome (WS) is a developmental disorder of genetic origin, with characteristic cognitive and personality profiles. Studies of WS point to an outgoing and gregarious personality style, often contrasted with autism spectrum disorders; however, recent research has uncovered underlying social reciprocity difficulties in people with WS. Social information processing difficulties that underlie these social reciprocity difficulties have been sparsely examined. Participants in the current study included 24 children with WS ages 8 through 15. A lab-based measure of social perception and social cognition was administered (Social Attribution Test), as well as an intellectual functioning measure (KBIT-II) and parent reports of communication and reciprocal social skills (Social Communication Questionnaire, Social Responsiveness Scale). Relations between social cognition, cognitive abilities, and social-communication were examined. Results demonstrated relations between parent-reported social reciprocity and the typicality of the responses provided in the lab-based measure, even once variability in intellectual functioning was taken into account. Specifically, those individuals who produced narratives in response to the social attribution task (SAT) that were more similar to those described in previous studies of typically developing individuals were also reported to have fewer social reciprocity difficulties in the real world setting as reported by parents. In addition, a significant improvement in performance on the SAT was seen with added scaffolding, particularly for participants with stronger intellectual functioning. These findings indicate that difficulties interpreting the social dynamics between others in ambiguous situations may contribute to the social relationship difficulties observed in people with WS, above and beyond the role of intellectual functioning. Exploratory analyses indicated that performance by individuals with stronger intellectual functioning is improved with additional structure to a greater degree than for those with weaker intellectual functioning. Interventions that specifically target these social information processing of individuals with WS would likely be beneficial.

Keywords: Williams syndrome, social cognition, social reciprocity, behavioral phenotype, social attribution task

INTRODUCTION

Williams syndrome (WS) is a neurodevelopmental disorder of genetic origin, specifically resulting from the deletion of approximately 25 genes on chromosome 7q11.23 (Ewart et al., 1993; Hillier et al., 2003). Individuals with WS typically display a distinctive cognitive and personality profile. In terms of a cognitive profile, results of numerous studies have pointed to some degree of developmental delay in the majority of patients (Udwin and Yule, 1991; Greer et al., 1997; Mervis et al., 2000), with a pattern of relative strengths and weaknesses, including relatively stronger language, after a period of early delays, than would be expected given developmental level (Mervis and Bertrand, 1997; Mervis and Robinson, 2000) and a marked difficulty with visuospatial construction tasks (MacDonald and Roy, 1988; Wang et al., 1995; Mervis et al., 1999). The personality profile is characterized by high sociability and friendliness, as well as high levels of empathy (Dilts et al., 1990; Tomc et al., 1990; Gosch and Pankau, 1997; Klein-Tasman and Mervis, 2003). Particular genes have been identified as being influential in the development of certain physical and behavioral traits commonly seen in WS, including connective tissue and cardiovascular abnormalities (Ewart et al., 1993), distinctive craniofacial features (Osborne et al., 1999; Tassabehji et al., 2005), difficulties in visuospatial abilities (Frangiskakis et al., 1996), and lower cognitive abilities (Morris et al., 2003). It should be emphasized that while a characteristic profile for WS is indicated by the literature, considerable variability within the cognitive and medical aspects of the profile alike have been reported (Morris et al., 1988; Udwin and Yule, 1991; Greer et al., 1997).

The vast majority of behavioral studies of people with WS describe a gregarious and socially outgoing personality type yet social difficulties are also characteristically seen (see Mervis and Klein-Tasman, 2000 for a review). Individuals with WS have been described as being less hesitant to interact with strangers than other children with developmental delays (Mervis et al., 2003),

as well as overly friendly and affectionate (Tomc et al., 1990). The presence of these overfriendly personality traits and the perception of preserved social functioning have often led to WS being compared with autism spectrum disorders (ASDs; Rapin and Tuchman, 2008), as a contrast to the severe reciprocal social impairment characteristic of ASD (American Psychiatric Association, 2000). However, a growing body of research, summarized and discussed in the following paragraphs, has begun to suggest that social skill difficulties are present in WS, such that comparisons with ASD may be less than optimal for contributing to advances in the neuroscience of social functioning unless a more nuanced approach is taken. The present study aims to investigate the social cognitive difficulties of individuals with WS (using a lab-based measure of social cognition) that may contribute to socio-communicative and reciprocal social interaction difficulties reported by parents.

Results of studies using parent- or caregiver-completed questionnaires have revealed difficulties in various aspects of social functioning in WS. For example, Laws and Bishop (2004) reported that parents consistently rated their children with WS as performing worse on measured aspects of relationship building when compared to healthy children or those with Downs syndrome (DS) or specific language impairment (SLI; e.g., inappropriate initiation of conversation, use of stereotyped conversation). In a similar study using the same measure, children with WS showed stronger functioning than those with ASDs (Philofsky et al., 2007). In terms of social skills, parents and teachers report that children with WS typically demonstrate prosocial skill levels (e.g., cooperation, assertion, seeking out interaction) within the low average range, with more pronounced difficulty with various aspects of social functioning and social cognition apparent (Klein-Tasman et al., 2011). Studies of older individuals with WS suggest that social difficulties persist into adulthood. Generally, adults with WS are found to experience trouble making and sustaining relationships despite their tendency to be socially disinhibited and overly friendly (Udwin, 1990; Davies et al., 1998). It seems as if individuals with WS are generally interested in making friends and driven to be socially accepted but lack the understanding of social rules that would allow for successful relationships. Unfortunately, these social difficulties may become more severe with development and represent the most consistent and pervasive difficulties seen in WS (Howlin et al., 1998).

Direct observations of social interactions in individuals with WS have also revealed difficulties. Delays in the use and comprehension of pointing gestures have been observed both by parent report and in structured laboratory settings (Singer Harris et al., 1997; Laing et al., 2002). Eye gaze differences have also been reported in WS, including an interest in faces that often interferes with completion of a task presented to the child (Jones et al., 2000). Young children with WS spend more time looking at faces of social partners than do typically developing children and the quality of the gaze is often described as "intense" (Mervis et al., 2003). Preschool aged children with WS have been shown to lack social regulation. Parents report that they know no stranger, and they are more willing to approach a stranger than typically developing children of the same chronological and mental age (Dodd et al., 2010). Young children with WS are also impaired in joint attention behaviors, both in terms of initiation of and response to joint attention bids (Laing et al., 2002). Although young children with WS appear to be more responsive to displays of emotion in comparison to other children with developmental delays, this increased responsiveness does not necessarily translate to an advantage in the ability to respond adaptively in ways that are congruent with the emotions expressed (Fidler et al., 2007). Difficulties in interactions with others, such as less turn-taking with partners (Lacroix et al., 2007) and a failure to completely answer questions or provide clarifications (Stojanovik et al., 2001; Stojanovik, 2006), are also often observed.

Recent studies using a measure specifically designed to investigate difficulties in reciprocal social interaction in ASD, the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 1999), have contributed to the growing understanding of social impairment in WS. Using the ADOS, Klein-Tasman et al. (2007) recently reported that approximately half of the children they examined (with limited language) exhibited abnormalities in the use of various social interactive behaviors, including eye gaze, pointing behaviors, both initiation and response to joint attention, integration of eye gaze with communicative behaviors, and reciprocal social smiling. Abnormalities in play behavior and repetitive and restricted interests were also apparent in many of these children. Further, when compared to children with developmental delays of mixed etiology (ME) and children with Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS), many young children with WS display a behavioral profile that indicates social difficulties above and beyond what would be expected from developmental delay alone (Klein-Tasman et al., 2009).

Although social difficulties in WS have been well-documented, findings of investigations into cognitive processes related to social functioning in WS have been inconsistent and inconclusive. For example, findings in the area of face processing are mixed, with some studies concluding that individuals with WS use unique strategies to process faces (Deruelle et al., 1999; Gagliardi et al., 2003), while others find contradictory support for the use of typical strategies (Tager-Flusberg et al., 2003). Similarly, findings related to eye movement patterns while visually processing faces differ depending on the specific aspect investigated. After initially fixating in a typical fashion, individuals with WS demonstrate a decreased ability to disengage attention and spend more time looking at faces when compared to healthy controls (Riby and Hancock, 2008, 2009a). Interestingly, this difference in gaze patterns was observed when stimuli were static, but not when they were active (Riby and Hancock, 2009b), demonstrating the importance of stimulus choice. Despite a tendency to look longer at faces, individuals with WS demonstrate decreased physical arousal while viewing faces when compared to typically developing groups (Doherty-Sneddon et al., 2009). This is consistent with a complementary finding in which individuals with WS were reported to perceive physical situations as more threatening than social situations (Dodd and Porter, 2010). Investigations into theory of mind abilities in WS do not yield straightforward findings. Adults with WS seem to outperform individuals with other developmental delays on some tasks (Karmiloff-Smith et al., 1995; Tager-Flusberg et al., 1998), while children perform both similarly to and worse than comparison groups on others (Tager-Flusberg and Sullivan, 2000). Generally, people with WS have difficulties on these social

cognitive tasks in comparison to TD controls, but it is unclear whether these difficulties are above and beyond what would be expected based on intellectual disability alone.

Task variability and diversity of contrast groups may contribute to the disparate findings in the literature, but it is clear from the discrepancies across studies that findings about social cognition in WS do not paint a straightforward picture. As is the case for both cognitive functioning and medical findings (Morris et al., 1988), there appears to be considerable variability in reciprocal social functioning within the WS population, with some, but not all individuals with WS demonstrating elevated social reciprocity difficulties. For example, Klein-Tasman et al. (2007) reported that half the children in their sample had elevated levels of social reciprocity difficulties, while half either showed very subtle social reciprocity difficulties or did not show any clear social reciprocity difficulties. The picture is further complicated by the lack of studies investigating the concordance between caregiver-reported behavior in everyday contexts and performance on tasks completed in a structured laboratory setting. Generally, studies have used either questionnaire or observational/experimental methodologies, rather than combining these approaches. Consistent findings across measures also constitute within-study replications of observations and build confidence in the reliability and validity of findings. Investigations examining the convergence between multiple methods of assessing a specific phenomenon contribute to the ecological validity of research conclusions. Finally, this research contributes to the literature exploring potential social information processing mechanisms for the social difficulties observed in children with WS; such studies of this nature may reveal target areas for intervention.

One measure of social information processing that has been used in the ASD literature but has not yet been used with children with WS is the Social Attribution Task (SAT; Klin, 2000). This task, adapted from Heider and Simmel's (1944) silent movie in which geometric shapes enact a social scene, measures the ability to attribute social meaning to a visually presented ambiguous animation. This task calls for inference of emotions, intentions, the nature of interpersonal interactions, and outcomes of interactions by anthropomorphizing the stimuli and reading non-verbal social cues. In Heider and Simmel's (1944) original description, they reported that all but one of the typically developing individuals who completed the task attributed human behaviors and emotions to the stimuli. Klin's coding scheme uses a number of indices, which are combined in order to provide a picture of broad social cognition (Klin, 2000, p. 836). More recent research using typically developing samples showed that completion of the SAT activated brain regions commonly implicated in social information processing (Schultz et al., 2003). In clinical samples, performance on the SAT was able to discriminate populations with documented social difficulties (i.e., ASDs and Prader-Willi Syndrome, PWS) from those without social impairments (Klin, 2000; Koenig et al., 2004; Klin and Jones, 2006). The video was described as "more meaningful to the normal control group, allowing [them] to generate fairly elaborated and lengthier social plots" (Klin, 2000, p. 839). These findings indicate that the SAT is an effective measure of social cognition, or more specifically the ability to attribute social meaning, including inference of common social interaction patterns and emotions, to seemingly ambiguous stimuli. Together these findings imply that this measure may be useful to further understanding social cognitive functioning in WS as well.

The current study sought to address gaps in the literature by examining the relations between social cognition and parent ratings of social reciprocity and social communication. Parent report of reciprocal social behaviors outside the laboratory setting was collected and individuals completed a lab-based measure of social information processing, the SAT (Klin, 2000). Parent ratings were related to performance on the SAT in order to investigate the concordance across measurement methodologies and to point to potential social information processing difficulties that may contribute to social reciprocity difficulties. The SAT has previously been used in individuals with ASD and was chosen based on the existing literature demonstrating its ability to differentiate clinical samples from one another (Klin, 2000; Koenig et al., 2004; Klin and Jones, 2006; see Materials and Methods for a more in-depth discussion), as well as its relation to activation in typically developing individuals of brain areas related to social cognitive processes (Schultz et al., 2003). We hypothesized that socio-communicative difficulties reported by parents would be associated with greater atypical social cognition, and weaker cognitive ability, especially verbal ability, would be associated with greater difficulty completing a laboratory based task of social cognition. We also considered the possibility that, given the intellectual disability commonly seen in WS, additional structure and support when completing the SAT, in the form of direct questioning, could be beneficial. We therefore created a direct measure of improvement within the SAT coding procedure, the Improvement Index, to quantify the difference in the quality of the narratives produced with prompting from those produced spontaneously. Using this index (further described later), exploratory analyses of the role of additional scaffolding on social attributions were conducted and related to overall intellectual functioning in order to further explore the role that cognitive abilities played in completion of the SAT.

MATERIALS AND METHODS

PARTICIPANTS

The sample included 24 children with WS between the ages of 8 years 1 month and 15 years 9 months ($M = 12$ years 5 months, SD = 2 years 8 months; 12 male, 12 female). Twenty-three female caregivers (22 mothers and 1 grandmother) and 1 father completed the questionnaires. Participants were recruited to participate in a study of cognitive and psychosocial functioning during the transition to adolescence. Participants were recruited by mailing fliers to families with children in the target age range through the Williams Syndrome Association, and by placing a description of the study in the registration materials at the National Williams Syndrome Convention. Note that this sample is a subset of the sample reported in Klein-Tasman et al. (2011).

MATERIALS

Standardized intelligence measure

Kaufman brief intelligence test, 2nd edition (KBIT-2). The KBIT-2 is a standardized measure of verbal and non-verbal intelligence for use with individuals ages 4–90 years. The verbal

intelligence scale (VIQ), which consists of two tasks measuring receptive and expressive language skills, is a measure of crystallized intelligence; the non-verbal scale (NVIQ), which involves solving visual puzzles, is a measure of fluid intelligence (Kaufman and Kaufman, 2004). Not only is this instrument one of the most commonly used brief estimates of intelligence, its use with individuals with WS is common as it does not include a spatial component, a set of skills that are often impaired in this population and therefore disproportionately affects IQ estimates (Mervis et al., 1999).

Experimental measure

Social Attribution Task. The SAT is a lab-based measure of social cognition utilizing ambiguous visual stimuli (Klin, 2000). Completing the SAT involves watching a silent video display, approximately 50 s long, two times through and providing a narrative summarizing the video. The individual is then shown shorter clips of the 50-s video and asked to narrate the clips separately. Finally, the individual is asked specific questions about the video. The ambiguous stimuli in the video are shapes (a small circle, a small triangle, and a large triangle) with no faces or other features similar to humans or other animals. These shapes move around the screen throughout the duration of the video. A more detailed description of instructions and prompts used in the SAT administration is included in the Section "Procedure."

Parent report measures

Social communication questionnaire (SCQ). The SCQ is a 40-item parent questionnaire for use with children ages 4 and older. The responses that caregivers provide about their children's social communication behaviors yield a total score. Scores above 15 points indicate social-communication difficulties that warrant further assessment for the presence of an ASD. This questionnaire is meant to serve as an efficient method of identifying children with communication and social delays (Rutter et al., 2003).

Social reciprocity scale (SRS). The SRS is a 65-item parent questionnaire for use with children ages 4–18 years used to explore symptoms of ASDs, including difficulties in interpersonal relationships, communication, and repetitive/stereotypic behaviors. Not only is the identification of these symptoms useful when screening for ASDs in particular, but can also be helpful in identifying individuals with problem behaviors in these domains that are at subthreshold levels. The responses that caregivers provided about their children's social reciprocity behaviors yielded *T*-scores on various scales of the SRS. These include the Social Awareness, Social Cognition, Social Communication, Social Motivation, and Autistic Mannerisms scales, as well as an overall total score. *T*-scores below 60 indicate no clinically significant concerns in social reciprocity behaviors; *T*-scores of 60–75 indicate social reciprocity difficulties that are in the mild to moderate range; *T*-scores greater than 76 indicate severe levels of social reciprocity difficulties (Constantino and Gruber, 2005).

PROCEDURE

DATA COLLECTION

Children participated either at the Child Neurodevelopment Research Lab (CNRL) at the University of Wisconsin, Milwaukee, in a quiet location at their homes, or in a quiet location at a Williams Syndrome Association Bi-Annual Meeting. All children were administered a battery of assessment measures, including a standardized measure of intelligence (KBIT-2) and other standardized and lab-based measures, including the SAT, over the course of an approximately 2 h long session. Parents of children completed questionnaires and interviews regarding anxiety symptoms and adaptive functioning either in a separate room or at a different time. All components of the child assessment were videotaped to review the procedure and allow for transcription of responses to the SAT.

SAT administration and coding procedures

Administration and subsequent coding procedures for the SAT followed those described by Klin's (2000). All administrations of the SAT were initially transcribed from videotape by an undergraduate research assistant in the CNRL and then reviewed by the author for accuracy. The first author and two research assistants initially coded four administrations and agreement between coders was measured using correlational statistics. Disagreements were discussed in order to improve reliability. Another four administrations were then coded and agreement between coders was measured. At this point, agreement was acceptable (Pertinence Index $r = 0.913$, Salience Index $r = 0.866$, Theory of Mind Cognition Index $r = 0.980$, Theory of Mind Affect Index $r = 0.908$, Animation Index $r = 0.718$, Problem Solving A Index $r = 0.982$, Problem Solving B Index $r = 0.967$, Improvement Index $r = 0.993$). The first author then coded all transcripts and the two research assistants each coded a portion of the transcripts, resulting in each administration being coded twice. Consensus coding was then conducted in order to resolve any disagreements and arrive at a single value for each index.

The Salience, Pertinence, and Animation indices, as well as the Theory of Mind Cognition and Affect indices were coded. See **Table 1** for a brief overview of coding procedures information. The Salience Index is a reflection of the individual's ability to make a coherent social story from visual information that fits in with what the majority of other individuals see in the same task. It serves as an estimation of the individual's overall ability to view the ambiguous stimuli and extract social information from what they see. In a real world setting, this would be similar to a situation in which an individual must make decisions about the behaviors of others and determine their meaning within a social context. The Pertinence Index is a measure of an individual's ability to make attributions that reflect relevance to the viewed stimuli. It is an estimation of the individual's ability to view stimuli and extract relevant information; this ability relates to real world social functioning, in which individuals need to determine exactly what information is socially relevant. The Animation Index is similar to a summary measure of social attribution; it reflects an estimation of the individual's overall level of social cognitive ability. Two Theory of Mind indices, Cognition and Affect, were also included in this investigation. These indices measure the frequency of references to cognitive or affective mental states, reflecting attention to the thoughts and feelings of others, a critical component when discussing the construct of theory of mind and understanding the nature of social interactions in general.

Table 1 | Overview of coding procedures.

Index	Narratives	Description	Measurement
Pertinence	1–7	Ratio of non-pertinent statements to total propositions	0.00–1.00
Salience	1–7	Percentage of correctly identified story elements out of 20 salient story elements	%
Theory of mind – cognitive	1–7	Ratio of number of statements indicating thinking, planning, or intentionality to total propositions	0.00–1.00
Theory of mind – affective	1–7	Ratio of number of statements indicating feeling states to total propositions	0.00–1.00
Animation	1–7	Ordinal rating of sophistication of social cognition	0–6
Problem solving	11–17	Percentage of questions answered correctly	%

Adapted from Koenig et al. (2004).

In addition to these indices, reported in Klin's original investigation, a novel index, the Improvement index was also coded to investigate the effect of providing greater structure during completion of the SAT. SAT administration guidelines involve first having the respondent describe what is seen with minimal prompts, and later specific prompts are provided to elicit elaboration. Arriving at a score for the Improvement index involves coding the Problem Solving index twice. The first time it is scored using the spontaneous answers the individual provides to open-ended questions during the initial administration of the SAT. It is then scored again using the answers the respondent provides in response to the more directed questions the examiner asks. For example, when first completing the administration, the examiner simply asks "What happened here?" after each clip is shown. However, when specific instructions are given, the examiner says, "Now let's say that the big triangle, the small triangle, and the circle are people. What kind of person is the big triangle? the small triangle? the circle?" The difference in the number of "correct" answers the individual provides in these two situations is then the score for the Improvement index.

RESULTS

All analyses were conducted using SPSS computing software. Significance tests were 2-tailed. It should be noted that all 24 children completed the intelligence measure and the SAT, while 21 had parent questionnaire data. All available data were used for each analysis.

INTELLECTUAL ABILITIES

The average overall IQ composite standard score, as measured with the KBIT-II, was 65.71 (SD = 11.99), with verbal and non-verbal IQ not significantly different from one another ($M = 73.08$, SD = 11.96 and $M = 66.29$, SD = 13.56, respectively). These results indicate that, on average, the current sample's intellectual functioning is falling in the mildly impaired range, which is consistent with the level of functioning and range seen in individuals with WS in other studies.

SOCIAL RECIPROCITY

Average *T*-scores and SDs for each domains are reported in **Table 2**. The number of children with *T*-scores falling within different classifications on the various domains is reported in **Figure 1**. The pattern of results indicates that on average, the children in this sample had mild to moderately elevated total scores, with the most severe difficulties in the area of Social Cognition and average range scores in the Social Motivation domain. Further discussion of these findings, demonstrating clear social reciprocity difficulties and good concordance between parent and teacher ratings, can be found in a separate publication from our lab (Klein-Tasman et al., 2011).

Table 2 | Parent-reported social reciprocity skills.

SRS domain	Mean *T*-score	SD
Social awareness	64.48	11.17
Social cognition	76.05	11.29
Social communication	66.86	10.55
Social motivation	55.24	15.92
Autistic mannerisms	75.05	15.10
Total score	70.24	11.17

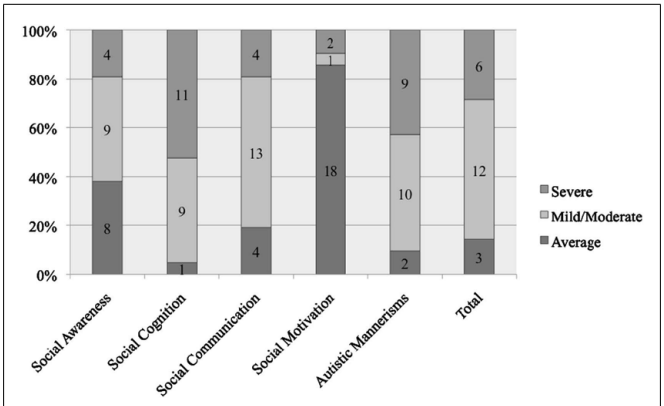

FIGURE 1 | Percent of participants falling in the average, mild/moderate, and severe ranges on the social responsiveness scale parent report measure (number of participants indicated).

SOCIAL COMMUNICATION

The average score on the SCQ in this population was 11.75 (SD = 6.39); however, what is more meaningful when interpreting this particular questionnaire is the number of children who met or exceeded the cutoff score of 15 and the relationship between meeting this cutoff and SAT performance. The distribution of scores on

the SCQ was continuous. In this sample, seven children (35%) met or exceeded the cutoff score, which indicates a need for additional screening for ASDs.

SOCIAL COGNITION

Mean scores for each of the indices of the SAT are reported in **Table 3**. Normative data are not available. The mean number of propositions spontaneously supplied in Narratives 1 through 7 was 20.71 (SD = 9.72). This number is generally similar to those reported in previous studies using clinical samples (Klin, 2000; Koenig et al., 2004). **Table 4** provides examples of different quality narratives supplied by participants in the current study.

RELATIONS BETWEEN SCQ AND SRS

Statistically significant and strong correlations were found between the total score of the SCQ and all domains of the SRS (Social Awareness $r = 0.768$, $p < 0.01$; Social Cognition $r = 0.707$, $p < 0.01$; Social Communication $r = 0.652$, $p < 0.01$; Autistic Mannerisms $r = 0.702$, $p < 0.01$; total $r = 0.837$, $p < 0.01$), with the exception of the Social Motivation domain ($r = 0.375$, ns). Given the outgoing nature of individuals with WS, as well as previous findings that individuals with WS do not have difficulty in the social motivation domain (Klein-Tasman et al., 2011), a weak correlation between the total score of the SCQ and the Social Motivation domain of the SRS was not unexpected.

Table 3 | Social Attribution Task (SAT) index scores.

SAT index	Mean	SD
Pertinence	0.36	0.30
Salience	3.33	2.62
Theory of mind – cognitive	0.06	0.12
Theory of mind – affect	0.03	0.06
Animation	1.46	0.72
Problem solving	0.21	0.19
Improvement	2.13	1.87

RELATIONS BETWEEN PERFORMANCE ON THE SAT AND INTELLECTUAL FUNCTIONING

Significant relations were found for the Pertinence index and VIQ ($r = -0.437$, $p < 0.05$) and the Problem Solving index and VIQ ($r = 0.446$, $p < 0.05$), NVIQ ($r = 0.416$, $p < 0.05$), and IQ composite score ($r = 0.544$, $p < 0.05$). The Improvement index was also significantly related to VIQ ($r = 0.398$, $p < 0.05$), NVIQ ($r = 0.578$, $p < 0.01$), and IQ composite score ($r = 0.628$, $p < 0.001$). There were no significant relations found for the Salience, Theory of Mind: Cognition, Theory of Mind: Affect, or Animation indices and score on the KBIT-II.

RELATIONS BETWEEN PERFORMANCE ON THE SAT AND AGE

There was a significant relation between age and performance on the Salience ($r = 0.403$, $p < 0.05$), Theory of Mind: Affect ($r = 0.402$, $p < 0.05$), and Problem Solving ($r = 0.448$, $p < 0.05$) indices. There was no significant relation between the age at which the SAT was administered and performance on the Pertinence, Theory of Mind: Cognition, Animation, or Improvement indices.

RELATIONS BETWEEN PERFORMANCE ON THE SAT AND PARENT-REPORTED SOCIAL RECIPROCITY

Significant relations between indices and *T*-scores on the domains of the SRS are reported in **Table 5**. All significant relations were negative, indicating that as scores on the SRS increased (suggestive of greater difficulty), scores on the SAT decreased (suggestive of greater difficulty). Scores on the Theory of Mind: Cognition Index were related to the Autistic Mannerisms scale. Scores on the Salience Index were significantly correlated with the Social Cognition, Social Communication, Social Motivation, and Autistic Mannerisms scales, as well as the overall total score. Scores on the Animation index were related to the Social Awareness scale and the SRS Total score. Scores on the Problem Solving Index were significantly correlated with the Social Awareness, Social Communication, and Autistic Mannerisms domain scores and the total score. Finally, scores on the Improvement Index were significantly related to the Social Awareness domain score. There were no significant relations found for the Pertinence and Theory of Mind: Affect indices of the SAT and any of the scales of the SRS.

Table 4 | Sample narratives.

Higher quality narratives	The smaller triangle and the circle came and went inside and was having fun and the triangle went out and was playing tag with the smaller one and then the circle kind of shut the door and the little one opened it and then the other one was still outside having fun and then the smaller circle and then the smaller triangle went out and the bigger triangle shut the box and destroyed it. What happened was like that triangle went through the triangle, I mean the square, and up . . . and all of the sudden the circle finally came in and closed the door on him and the triangle was stuck for a minute and the triangle got out and the triangle friend came in . . . so they were um both in the house and the triangle went out and slammed the door behind him so they were looking for each other and stuff and they came around and like together like walking and all of a sudden the triangle starts to chase him so the triangle and the circle go running across the screen and out of the picture and the triangle messes up the square kind of and that was it.
Lower quality narratives	I saw a circle, a square and a triangle. Sometimes umm the triangle will umm bump into another triangle and then sometimes the circle would bump into the triangle and sometimes the square would open and close and then umm at the end I saw two lines and that's it. . . . the big triangle chased the little triangle and the little ball goes there and then the triangle chased the triangle and the ball and then they went back that way and then went plew, right through it and that was it.

Table 5 | Correlations between SAT performance and parent-reported social reciprocity skills.

SAT index	Social responsiveness scale domain					
	Social awareness	Social cognition	Social communication	Social motivation	Autistic mannerisms	Total score
Pertinence	0.383	0.269	0.375	0.238	0.197	0.377
Salience	−0.342	−0.636**	−0.615**	−0.466*	−0.534**	−0.640**
Theory of mind – cognition	−0.143	−0.102	−0.191	−0.206	−0.432*	−0.268
Theory of mind – affect	0.059	−0.374	−0.300	−0.194	−0.381	−0.226
Animation	−0.459*	−0.269	−0.339	−0.299	−0.528**	−0.492*
Problem solving	−0.624**	−0.365	−0.487*	−0.249	−0.514*	−0.547**
Improvement	−0.480*	−0.100	−0.225	−0.108	−0.259	−0.272

$*p < 0.05$.

$**p < 0.01$.

Given the significant relations with intellectual functioning, partial correlations to examine the relationships between SAT indices and the SRS taking into account KBIT-2 IQ were conducted. Significant negative relationships remained between performance on the Salience index and the Social Cognition ($r = -0.613$, $p < 0.01$), Social Communication ($r = -0.561$, $p < 0.01$), Social Motivation ($r = -0.458$, $p < 0.05$), and Autistic Mannerisms scales ($r = -0.528$, $p < 0.01$) and the SRS total score ($r = -0.602$, $p < 0.01$). Negative relationships between the Animation index and the Autistic Mannerisms scale ($r = -0.515$, $p < 0.05$) and the Problem Solving Index and the Social Awareness ($r = -0.490$, $p < 0.05$) and Autistic Mannerisms ($r = -0.479$, $p < 0.05$) scales remained significant as well.

RELATIONS BETWEEN PERFORMANCE ON THE SAT AND PARENT-REPORTED IMPAIRMENTS ON A SCREENING MEASURE FOR ASD

Significant relations were found for the Salience Index and total score of the SCQ ($r = -0.457$, $p < 0.05$), as well as the Animation Index and total score on the SCQ ($r = -0.493$, $p < 0.05$) and classification on the SCQ ($r = -0.495$, $p < 0.05$). The Problem Solving index was also significantly related to total score on the SCQ ($r = -0.596$, $p < 0.05$) and classification on the SCQ ($r = -0.480$, $p < 0.05$). There were no significant relations found for the Pertinence, Theory of Mind Cognition, Theory of Mind Affect, or Improvement indices of the SAT and score on the SCQ. When intellectual functioning was taken into account using partial correlations, significant relations between SCQ classification and the Animation index ($r = -0.455$, $p < 0.05$) and the Problem Solving index ($r = -0.477$, $p < 0.05$) remained. The negative direction of these relationships indicates that as scores on the SCQ increase, reflecting greater difficulty, scores on the SAT decrease, also reflecting greater difficulty.

CHANGE IN SAT PERFORMANCE WITH THE ADDITION OF SPECIFIC INSTRUCTIONS

Participants were first asked to describe the scenes in the video without specific instructions; on average, only 4.17% of the "target" answers were spontaneously provided during these narratives. However, when the participants were given instructions as to how to view the stimuli, 21.25% of the "target" answers were provided. These instructions included directions as to how to view the shapes in the video (i.e., as people) and how to interpret the interactions they had (see Klin, 2000 for specific questions). In other words, when the individuals in this sample were provided with the additional specific instructions that are part of the SAT administration process about how to interpret the traits and actions of the previously ambiguous stimuli as socially meaningful, there was a significant change in the quality of the narratives they were able to provide [$t(23) = 4.833$, $p < 0.005$]. This improvement that was seen with the additional scaffolding was significantly related to overall level of intellectual functioning ($r = 0.628$, $p < 0.01$), such that those with stronger intellectual functioning showed larger improvements with scaffolding.

DISCUSSION

Both questionnaire and laboratory based studies have revealed difficulties in social reciprocity in children and adults with WS. However, few studies have used multiple converging measures in the same individuals to evaluate the relationship between informant report and observable behaviors seen in a laboratory setting and to explore the social information processing difficulties that may contribute to social reciprocity challenges. The goal of the current study was to carry out such an examination using a lab-based measure of social cognition and intellectual and parent-rated socio-communicative and social reciprocity functioning in children with WS. As hypothesized, results indicated a significant relationship between directly measured social processing abilities and reciprocal social behaviors in WS children as rated by parents. Intellectual functioning and social cognition were also found to be significantly related, however the modest strength of this relationship suggested that intellectual functioning alone does not explain SAT performance. Furthermore, significant relationships between social processing and reciprocal social behaviors remained after accounting for intellectual ability, suggesting that difficulties in social cognition have a unique role in the social reciprocity difficulties of individuals with WS.

RELATIONS BETWEEN SOCIAL COGNITION AND PARENT-REPORTED BEHAVIOR

Individuals with WS who were more adept at making social attributions were also rated higher in terms of parent-reported social reciprocity skills, motivation to engage in social activities, the ability to interpret social cues in the world, and the level of expressive social communication. Similarly, individuals with WS who provided answers that were more consistent with those provided by typically developing adolescents and adults (as reflected by higher ratings on the Problem Solving index) were rated as more aware of social cues in the real world. Essentially, individuals with WS who made more appropriate social attributions in this lab-based task were also rated by their parents as more socially aware and competent in their daily lives. This relationship is further supported by the findings of a strong correlation between the two parent report measures used and their similar relationship to the SAT. Specifically, both SCQ and SRS scores were correlated with the Animation and Problem Solving indices of the SAT, which are both reflections of common social interpretations of the ambiguous scenes.

As past reports have indicated, a proportion of individuals with WS have an interest in others while simultaneously lacking the appropriate skills necessary to sustain interactions and form lasting relationships (Davies et al., 1998; Laws and Bishop, 2004). The consistency and pervasiveness of this difficulty with relationships is actually one of the most frequently reported concerns of caregivers (Udwin, 1990). Based on studies using questionnaires or lab-based measures separately, individuals with WS have difficulty comprehending environmental cues that are important to social functioning, such as non-verbal aspects of language, or pragmatics (Philofsky et al., 2007) and perspective taking (Fidler et al., 2007). Klein-Tasman et al. (2011) found that while children with WS were reported to have social reciprocity difficulties, they were more related to difficulties in social cognition than in social motivation. These difficulties likely contribute to the decreased ability to establish and maintain meaningful relationships, despite superficially average overt social initiation skills. The results of the current study support the assertion that individuals with more pronounced social difficulties as reported by caregiver questionnaire are also more likely to have difficulties picking up on the typical social information relevant to social scenes, such as the various roles played by those participating in an interaction, the potential feelings and subsequent motivations for actions, and the consequences of those actions. When people with WS do not pick up on these aspects of others' social behavior, this likely contributes to difficulties with successful social interactions.

FACILITATIVE EFFECTS OF ADDITIONAL STRUCTURE

An additional exploratory aim was to examine the effect of additional structure on social attributions made by the participants. The vast majority of participants in this study were unable to produce narratives that spontaneously correctly answered even one of the obvious questions related to the stimuli. However, when asked directly about these aspects, participants were more able to provide answers that were consistent with previously identified normative answers (Klin, 2000). Moreover, the beneficial effects of specific questioning were more pronounced for participants with stronger intellectual functioning. The additional structure provided by asking specific questions is similar to the concept of scaffolding, a metaphor first discussed at length by Wood et al. (1976). Similarly to Vygotsky's zone of proximal development (Vygotsky, 1978), scaffolding refers to the structure and additional instruction that parents, teachers, and other caregivers provide when children are attempting to complete a task with components that are not yet at the level of mastery (Stone, 1998). The benefits of scaffolding for both typically developing children and those with developmental delays are widely acknowledged and studied. Specifically, the use of scaffolding has been shown to aid children with delays in the acquisition of language (Kirchner, 1991), the development of social skills (Baker et al., 2007), and in improving reading comprehension abilities (Dieterich et al., 2006). The current study, which includes participants with mild to moderate intellectual impairments, demonstrates the added benefits of scaffolding while completing a social cognitive activity. A significantly greater number of target responses were produced when the participants were given more explicit instructions about how to view the stimuli.

Given the importance of effective scaffolding, parent-training programs for children with developmental delays could focus on ways in which to structure the environment to ensure consistent skill acquisition. The benefits of scaffolding in the current study fit with these findings and may suggest that these types of interventions and additional structure may provide some individuals with WS (i.e., those with less severe cognitive impairments) with the additional resources needed to more effectively interpret ambiguous social stimuli and gain skills in social reciprocity. It appears as though the children in the current study with more severe intellectual impairments do not benefit from the additional structure provided; it is possible that the ambiguous stimuli, which are shapes that do not physically resemble humans or animals, were simply too abstract for them. These limitations to the benefit of scaffolding are important to keep in mind; interventions using more abstract materials may not in fact be beneficial even with additional structure.

LIMITATIONS AND FUTURE DIRECTIONS

The current study represents the first investigation into the performance of individuals with WS on the SAT, a lab-based measure of social cognition and attribution, and relations to behavioral and intellectual characteristics. Although a typically developing control group was not included, results revealed a number of relationships between social cognition abilities and parent-reported behavior. The inclusion of control groups in future investigations would allow for exploration of questions related to the developmental trajectories (i.e., delay or deviance) of social cognition in WS and further explore the potential influence of intellectual functioning. In particular, a contrast group of individuals with ASDs would allow for comparisons to a population with documented and consistent difficulties in social cognitive and social reciprocity skills. As was demonstrated in previous studies using the SAT (Klin, 2000; Koenig et al., 2004; Klin and Jones, 2006), individuals with ASDs have difficulty completing the task in comparison to both typical and clinical control groups, demonstrating an underlying difficulty in social cognitive processing. Direct comparisons to children with ASD would allow for further specification of the aspects of reciprocal social interaction difficulties that are also

shared by individuals with WS, and those aspects that appear to be less commonly seen in WS and differentiate WS from ASD. Regardless of the relations found, these types of investigations would provide a better understanding of the social cognitive difficulties that relate to the observable social difficulties in these two clinical populations and may even play a role in determining the presence of a comorbid ASD in individuals with WS. In addition, other contributors to performance on the SAT warrant examination. For example, it is possible that additional personality character traits, such as empathy and emotional responsivity, may contribute to SAT performance for children with WS.

The SAT was used as a way to add to the literature about social cognition in WS, and we have made some attempt to elucidate aspects of social cognition that are likely measured by the SAT. However, as is the case for other studies of social cognition, the current study is somewhat limited by a lack of a unifying theory as to what specific components contribute to skills that fall under the umbrella term "social cognition." Emotion recognition, face processing, empathy, and theory of mind abilities are just a few of the possible contributors to social information processing; a number of additional processes, including understanding of ambiguous social dynamics, also likely playing a part in social cognition and should be considered. The field would benefit from a well-defined and clearly outlined theory of social cognition that would allow for future studies to more explicitly explore mechanisms of reciprocal social behaviors and models of the relations among the various facets of social cognition.

The present study demonstrated relationships between the performance of individuals with WS on a lab-based measure of social cognition and various parent-reported socio-communicative abilities, as well as cognitive functioning. The significant relations observed point to underlying social cognitive processing difficulties that may contribute to social reciprocity behaviors observed in the natural setting outside of the laboratory, even once variability in intellectual functioning is taken into account. In addition, the results provide evidence that additional structure and support can potentially help individuals with WS, particularly those with stronger intellectual functioning, more effectively process social information. Further study of social information processing difficulties underlying the social reciprocity limitations of individuals with WS is warranted to point toward targets for effective intervention.

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Visual attention to dynamic faces and objects is linked to face processing skills: a combined study of children with autism and controls

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Although the extant literature on face recognition skills in Autism Spectrum Disorder (ASD) shows clear impairments compared to typically developing controls (TDC) at the group level, the distribution of scores within ASD is broad. In the present research, we take a dimensional approach and explore how differences in social attention during an eye tracking experiment correlate with face recognition skills across ASD and TDC. Emotional discrimination and person identity perception face processing skills were assessed using the Let's Face It! Skills Battery in 110 children with and without ASD. Social attention was assessed using infrared eye gaze tracking during passive viewing of movies of facial expressions and objects displayed together on a computer screen. Face processing skills were significantly correlated with measures of attention to faces and with social skills as measured by the Social Communication Questionnaire (SCQ). Consistent with prior research, children with ASD scored significantly lower on face processing skills tests but, unexpectedly, group differences in amount of attention to faces (vs. objects) were not found. We discuss possible methodological contributions to this null finding. We also highlight the importance of a dimensional approach for understanding the developmental origins of reduced face perception skills, and emphasize the need for longitudinal research to truly understand how social motivation and social attention influence the development of social perceptual skills.

Keywords: autism, eye tracking, face processing, eyetracking, autism spectrum disorder, ASD

INTRODUCTION

Face recognition is one of the more thoroughly studied skills in the field of autism research (Wolf et al., 2008; Tanaka et al., 2012; for a reviews see Harms et al., 2010; Weigelt et al., 2012). While some aspects of typical face recognition may be preserved among individuals with autism spectrum disorder (ASD; for example, aspects of holistic processing: Scherf et al., 2008; Faja et al., 2009), research on face identity recognition and facial expression recognition consistently reveal impairments relative to typically developing children (TDC; Wolf et al., 2008; McPartland et al., 2011; Tanaka et al., 2012).

Face processing is believed to be a universal domain of expertise in humans and perhaps one of the earliest to develop (Gliga and Csibra, 2007). Early functional specialization for faces during infancy contrasts with that of other categories of objects, such as body parts (Gliga and Csibra, 2007) and may result from special attention to social information throughout development, allowing for more perceptual discrimination and categorization experience with face stimuli. Evidence for this early attentional bias is robust. Classic studies have demonstrated that despite poor vision, newborns display a preference for looking at face-like stimuli within days or even hours after birth (Goren et al., 1975; Johnson and Morton, 1991) and recent research has highlighted that this attentional bias bears the signature of a domain-specific disposition to preferentially process faces (Rosa-Salva et al., 2010). Even if this bias is present from early in life in our species, individual differences in the prioritization of social information by attention and perceptual systems may yield individual differences in measured social perceptual skills later in childhood, thereby creating a continuum of skill within the population (Schultz, 2005; Russell et al., 2009).

Reduced attention to and motivation for engaging with face stimuli is a prominent hypothesis for why children with ASD might, on average, have reduced face perceptual skills (Schultz et al., 2000; Grelotti et al., 2002; Dawson et al., 2005; Chevallier et al., 2012a,b). According to this social motivation hypothesis, faces have a significantly less reward value for most children with ASD, leading to reduced social attention and diminished social experience which blunts the development of cortical specialization for faces (Grelotti et al., 2002; Johnson, 2005; Schultz, 2005). Reduced motivation is thus seen as ultimately depriving children with ASD of the visual experience needed to develop their face perception skills. This hypothesis is consistent with infrared gaze tracking studies showing that individuals with autism attend

more to the non-social than social features of static visual scenes (Riby and Hancock, 2008; Sasson et al., 2008). Similarly, in studies using dynamic movie clips, children, adolescents and young adults with autism fixate less on people, faces and eyes and more on objects than do typical controls (Klin et al., 2002; Nakano et al., 2010; Rice et al., 2012).

Differences in social attention appear to be one of the earliest signs of autism. For example, a preference for non-social patterns (e.g., geometric shapes) in toddlers is a robust risk factor for developing the disorder (Pierce et al., 2011), and differential electrophysiological responses to shifts in eye gaze at 6 months predict ASD group membership nearly 3 years later (Elsabbagh et al., 2012).

The present research aims to provide a more direct test of the link between social attention and face perception by examining spontaneous attention to faces and objects in participants occupying the entire face expertise continuum. Prior research using ASD and typical participants has focused on group means, overlooking within-group variability. An alternative approach is to ignore diagnostic categories and boundaries and adopt a more dimensional approach (Insel et al., 2010; Sanislow et al., 2010). Dimensional approaches are especially promising in the context of developmental models that propose links between observable behaviors and developmental outcomes.

In the present study, participants' gaze was tracked as they watched movies of actors showing different facial expressions and videos of non-social moving objects (e.g., a bulldozer pushing earth, clothes on a line flapping in the wind) in the same display. The four videos composed a 2 by 2 design, faces vs. objects that were either of high vs. low salience (e.g., faces gazing directly at the camera vs. averted; bulldozers vs. clothing). This study tested the following hypotheses:

1. Attention to faces correlates with face perception accuracy as measured by two subtests of the *Let's Face It!* Skills Battery across all participants.
2. Social skills (as measured by the SCQ) predict social attention and face perception skill.
3. On average, the ASD group will score lower on face perception tests and will spend less time attending to social information.

METHODS

PARTICIPANTS

We studied 110 children and adolescents, including 60 diagnosed with an ASD (7 female) and 50 typically developing controls (TDC; 12 female). ASD and TDC groups were matched on non-verbal cognitive ability as measured by the Differential Ability Scales, Second Edition (DAS-II, Elliot, 2007), gender ratio and chronological age (**Table 1**). Participants had no uncorrected auditory or visual impairment, known genetic conditions, history of TBI, premature birth, or other medical or neurological abnormality. All participants were native speakers of English. Members of the TDC group did not have a DSM-IV-TR Axis I disorder. Data validity across the eyetracking portion of the experiment was examined and inclusionary criterion required participant recordings to have a sampling rate above 80% (as calculated by the Tobii software). Initial screening for autism symptomatology was conducted using the Social Communication Questionnaire (SCQ; Rutter et al., 2003a,b) and severity of symptom presentation was documented using the Social Responsiveness Scale (SRS; Constantino and Gruber, 2005). SCQ lifetime scores were also used to test correlational hypotheses. Current diagnosis was confirmed by expert clinical judgment, based on parent-reported developmental history (Autism Diagnostic Interview-Revised: ADI-R; Rutter et al., 2003a,b) and symptom presentation (Autism Diagnostic Observation Schedule: ADOS; Lord et al., 2000). Within the ASD cohort, 52 children were given the ADOS module 3 and eight children were given module 4. Using the original ADOS algorithm (Lord et al., 2000), 31 scored in the autism range, 22 scored in the ASD range, and 7 children scored below ADOS diagnostic cutoffs (see **Table 2**), but nevertheless met criteria according to developmental history and expert clinical judgment (Lord et al., 2000). Total scores were also tabulated using the revised ADOS algorithm (Gotham et al., 2009) for those

Table 1 | Participant characteristics by diagnostic group.

	ASD ($N = 60$)	TDC ($N = 50$)	*t*-value	*p*-value
Mean age in years (SD)	11.28 (2.89)	11.34 (3.04)	0.10	0.92
Age range	6.17–17.92	6.33–17.92		
Mean GCA (SD)	111.63 (14.61)	113.70 (14.58)	0.74	0.46
GCA range	88–158	87–150		
Mean verbal (SD)	110.12 (16.61)	116.42 (16.70)	1.98	0.05
Verbal score range	77–161	89–165		
Mean non-verbal (SD)	111.07 (15.48)	108.26 (13.71)	−1.00	0.32
Non-verbal range	84–166	80–143		
Mean LFI score (SD)	78.83 (7.29)	82.70 (7.78)	2.69	0.008
LFI range	61.67–96.66	65.00–96.66		
Mean SCQ score (SD)	20.67 (5.61)	1.12 (1.29)	−24.11	0.000
SCQ range	11–34	0–4		
			Chi-Square	*p*-value
Sex: Male	53 of 60	38 of 50	2.90	0.09

Table 2 | Mean ADOS scores (original algorithm).

	Communication mean (SD)	Social interaction mean (SD)	Total mean (SD)
Module 3 ($N = 52$)	2.94 (1.29)	7.08 (2.73)	10.02 (3.69)
Module 4 ($N = 8$)	3.57 (1.72)	7.13 (1.46)	10.50 (2.83)

A communication score of 2 indicates ASD, and 3 or above indicates autism. A social interaction score of 4 or 5 indicates ASD, and 6 or above indicates autism. Total scores of 10 or above indicate autism; total scores of 7 or above indicate ASD.

individuals who received module 3 of the ADOS (currently, no revised algorithm exists for module 4). Based on the revised algorithm, 37 participants scored within the autism range, 7 scored within the ASD range, and 8 scored below cutoffs. Each revised algorithm score was converted to a standardized autism symptom severity score, following the procedures described by Gotham and colleagues (2009). When using this symptom severity metric, 8 participants were classified as non-spectrum, 6 ASD, and 38 AUT (autism). All assessment measures were administered, scored, and interpreted by a clinical psychologist or supervised doctoral level psychology trainee who met standard requirements for research reliability.

MEASURES AND DESIGN

The *Let's Face It!* Skills Battery (LFI; Wolf et al., 2008; Tanaka et al., 2012) is composed of 11 separate computer-administered tests, guided by contemporary theories of face perception processes. It assesses face recognition abilities in two broad domains involving (1) the perception of person identity and (2) the perception of facial expression. These constructs have been validated in other samples using principal components analyses (Wolf et al., 2008). Previously, Wolf and colleagues (2008) and Tanaka and colleagues (2012) found robust deficits (standardized effect sizes ranging from 0.40 to 1.0 SD) in both person and emotion identity using a common large sample (∼66–85 individuals with ASD and 66–140 TDCs) across nearly all measures in the battery (significant). These tests are reliable (split half reliabilities >0.75) and have large normative (by gender and IQ) datasets from ages 6 to 18 (see Wolf et al., 2008). Based on this prior research, we chose the two LFI subtests which best discriminated the groups on face identity and face expression discrimination.

a. The Matching Identity Across Expression subtest evaluates a child's ability to recognize facial identities across changes in expression (happy, angry, sad, disgusted, and frightened). A target face is shown alone for 500 ms, followed by three probe faces of different identities presented simultaneously with the target face. Children must select the face that matches the target's identity ignoring the fact that the expression is different.
b. The Matchmaker Expression subtest assesses the child's ability to match emotional expressions across different identities. Five basic emotions (sad, angry, happy, frightened, and disgusted) were tested. A target face depicting a basic emotion in frontal profile was shown alone for 1000 ms and then remained on the screen as three probe faces of different identities conveying different expressions were presented. Children must select the face with the expression that matches the target.

Eye-tracking task

Participants were calibrated at the beginning of the experiment using a standard five-point calibration procedure. The experiment included twelve 15-s trials consisting of four silent videos playing concurrently, one in each quadrant of the screen (pseudo-randomized location). In order to minimize the predictability of the display, a jitter was introduced so that the videos were not consistently placed right in the center of each quadrant. The distance in pixels from the center of the screen to the mid-point of each image did not differ between conditions [Face clips $M_{(SD)} = 575(53)$px; Object clips $M_{(SD)} = 593(38)$px; $t_{(46)} = -1.69$, $p = 0.10$]. The videos subtended approximately 20 degrees of visual angle horizontally and 14 degrees of visual angle vertically. The four videos shown on the screen in each trial consisted of (1) a face gazing directly at the camera, (2) a face averted from the camera (faces matched for sex), (3) a highly salient object, and (4) an object with lower salience. Face clips displayed emotions, which were the same within trial but different across trials. Twenty-four different faces were used (12 male, 12 female). Of the two faces in each trial, one faced the camera directly and was considered "high salience." The other face was averted, and was considered "low salience." Twenty-four different objects were included. Of the two objects in each trial, 12 were "high salience" including objects such as trains and airplanes (South et al., 2005). Twelve were "low salience" and included objects such as clothes and flowers. Each individual video clip lasted 3.75 s and was looped 4 times during the 15-s trial, so that children could look at each of the four clips and still get all of the visual information available in each clip. Trials were separated by a 1-s crosshair in the center of the screen (see **Figure 1**). Dynamic video stimuli fit a 2 × 2 design with Type (face/object) and Salience (high/low) as within-group factors.

PROCEDURE

At the beginning of each study visit, parents provide informed consent for their child; participant assent was obtained when feasible. Next the DAS-II and the ADOS were administered to the child while parents completed the ADI-R. After a lunch break, children completed the eyetracking task and the LFI tasks. Eye tracking took place in a quiet room containing a chair and a 30-inch computer screen on an adjustable table. A Tobii X120 gaze tracker recorded participants' looking patterns at a rate of 60 Hz from a seated distance of approximately 60 cm. Above the computer monitor, a webcam simultaneously recorded a video of

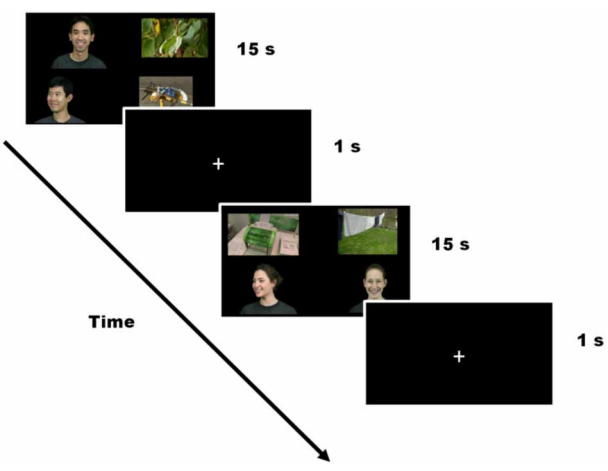

FIGURE 1 | Schematic representation of the experiment.

the participant. Participants were informed that they would see a few short videos, and were asked to watch the screen.

All participants and parents received oral feedback at the time of the visit, as well as a written report, and compensation for time and travel. The Institutional Review Board at The Children's Hospital of Philadelphia approved all procedures related to this project.

PRELIMINARY ANALYSES: *Let's Face It!* SKILLS BATTERY

Accuracy scores from the two *Let's Face It!* Identity and Expression subtests were averaged and examined for normality across 119 participants with and without ASD. Eight participants with the lowest scores (2 TDC, 6 ASD) and 1 with the highest score (TDC) were excluded as outliers. The remaining 110 participants had scores on the composite metric of face processing skills that met normality assumptions (**Table 1**; Shapiro-Wilk = 0.99, $p = 0.26$). Diagnostic group differences were found in the final sample such that TDC scored significantly higher ($M = 82.70$, $SD = 7.78$) than ASD ($M = 78.83$, $SD = 7.29$), $t_{(108)} = 3.87$, $p = 0.008$, Cohen's $d = 0.51$. This size of this difference is smaller than the one found by Tanaka and colleagues, for at least two reasons: First, children in the present study were included only if their Tobii sampling rate was above 80%, which already differentiates our sample from the original. However, a high sampling rate cutoff is required for accurate gaze data (which is a primary focus of our analyses). Second, eliminating outliers as necessary for the regression analyses we planned to run reduced variability and the size of the LFI group difference. Despite these limitations, the group difference in face processing as measured by the LFI was still of moderate effect size.

ANALYSES

Eye tracking

Tobii software produces a variable called Total Fixation Duration, which is the sum total length of all fixations within a given AOI. It is often used as a measure of preference for looking at one stimulus type over another (Klin et al., 2002; Nakano et al., 2010; Rice et al., 2012). Given our hypothesis that the amount of time spent attending to a stimulus relates to the development of expertise in that stimulus type, we focused on Total Fixation Duration in our analyses. To control for individual variations in overall looking and to account for differences in AOI size, we calculated the Proportion of Total Fixation Duration by dividing the time spent looking at each AOI (high salience face, low salience face, high salience object, low salience object) by the total amount of time looking at all AOIs.

Statistics

Two types of analyses were performed. First, linear regressions were constructed to assess whether social attention predicts face processing skill and gaze to faces. Preliminary analyses revealed that age was significantly correlated with face processing skills (Pearson's $r = 0.49$, $p < 0.001$), so chronological age was entered in the first step of the regressions to control for its effect on face expertise. Second, a 2 (stimulus: face/object) × 2 (salience: high/low) × 2 (diagnostic group: ASD/TDC) repeated measures ANOVA explored whether gaze patterns differed for high- and low-salience stimuli, and whether looking patterns to faces and objects differed by diagnostic group. Stimulus type (face, object) and salience (high, low) were entered as within-subjects variables and diagnostic group (ASD, TDC) was entered as a between-subjects factor. Effect sizes (partial eta-squared, η_p^2, for F statistics and Cohen's d for t-tests) are reported together with p-values for significant main effects and interactions, and *post-hoc* t-tests are Bonferroni corrected to require a significance value of $p < 0.01$. A η_p^2 value above 0.01 is typically considered to reflect a small effect, a η_p^2 above 0.06 to reflect a medium effect, and a η_p^2 above 0.14 to reflect a large effect. Cohen's d values above 0.20, 0.50, and 0.80 are considered to reflect small, medium and large effects, respectively. The directionality of effects revealed by the omnibus ANOVA is determined using paired- and/or independent samples t-tests as appropriate.

TEST–RETEST RELIABILITY OF THE EYE-TRACKING MEASURE

Forty-two different participants (23 with ASD, 19 TDCs, all male, average age = 15.03 years, average IQ = 105.45) were recruited using the criteria described in the participant section above. These participants were asked to complete the eye tracking experiment at two time points separated by a 9-week interval (±1 week). An intraclass correlation coefficient (ICC) was computed using a two-factor mixed-effects consistency model (Farzin et al., 2011). An intraclass correlation >0.40 is considered good, and >0.75 is excellent. Test–retest reliability for the proportion of total fixation duration to faces at Time 1 and Time 2 was good to excellent (single measures ICC = 0.69, $p < 0.001$).

RESULTS

DOES GAZE TO FACES PREDICT FACE EXPERTISE?

The Social Motivation theory of autism argues that varying levels of social motivation modulate experience with faces over the course of development, and ultimately impact children's face processing skills. A two-step multiple regression analysis was therefore used to discern whether visual attention to faces predicts face perception skill in the combined sample of ASD and TDC participants. Age was entered in Step 1, as preliminary analyses suggested that face processing skills are positively correlated with chronological age (Pearson's $r = 0.49$, $p < 0.001$) and prior research suggests that face expertise continues to develop throughout childhood and adolescence (Carey et al., 1980; Thomas et al., 2007). Proportion of total fixation duration to faces was entered into the model in Step 2. Consistent with our hypothesis, attention to faces accounted for a significant amount of variance in face processing skills above and beyond the effect of age, $\Delta F_{(1,\ 107)} = 5.64$, $p = 0.02$ (**Table 3**, **Figure 2A**).

Next, we tested whether scores on the SCQ (a measure that evaluates autistic symptomatology, including social communication skills) predicted total fixation duration to faces and face perceptual skills. While the SCQ not a measure of social motivation *per se*, these analyses may serve as a springboard for future targeted research using a scale designed specifically to assess motivation. A regression entering SCQ total score as a predictor of attention to faces returned a null result. Next, to test the relationship to face perception skill, we conducted a regression with age entered in Step 1 and SCQ entered in Step 2. Results revealed

that the SCQ score accounts for a significant amount of variance in face processing skills after accounting for the effect of age, $\Delta F_{(1,\ 107)} = 23.92$, $p < 0.001$ (**Table 4**, **Figure 2B**), with greater social impairment being associated with reduced face expertise.

To determine whether total fixation duration to faces differed by stimulus type, salience level, and diagnostic group, a 2 (Type: face/object) × 2 (Salience: high/low) × 2 (Diagnosis: ASD/TDC) repeated measures ANOVA was conducted. This analysis revealed a main effect of Type, $F_{(1,\ 108)} = 61.63$, $p < 0.001$, $\eta_p^2 = 0.36$, a main effect of Salience, $F_{(1,\ 108)} = 131.07$, $p < 0.001$, $\eta_p^2 = 0.57$, and an interaction between Type and Salience, $F_{(1,\ 108)} = 44.17$, $p < 0.001$, $\eta_p^2 = 0.30$. Contrary to our hypothesis, however, there was no effect of Diagnosis, either as a main effect or as an interaction with Type [$F_{(1,\ 108)} = 0.13$, $p = 0.72$, $\eta_p^2 = 0.001$], Salience [$F_{(1,\ 108)} = 1.81$, $p = 0.18$, $\eta_p^2 = 0.02$], or Type x Salience [$F_{(1,\ 108)} = 0.27$, $p = 0.60$, $\eta_p^2 = 0.003$]. *Post-hoc* tests revealed that all participants looked significantly more at objects (63%) than at faces (37%), $t_{(109)} = -7.95$, $p < 0.001$, and more at high salience stimuli (direct faces and high salience objects, 59%) than low salience stimuli (averted faces and low salience objects, 41%), $t_{(109)} = 11.58$, $p < 0.001$. Diagnostic group differences were not significant: participants with ASD looked at faces 36% of the time compared to 38% of the time in the TDC group, $t_{(108)} = 0.37$, $p = 0.72$, and at high salience stimuli (direct faces and high salience objects) 60% of the time compared to 50% in the TDC group, $t_{(108)} = 1.35$, $p = 0.18$. Interestingly, gaze to direct and averted faces was tightly correlated across groups (direct: 20%, averted: 17%, $r = 0.73$, $p < 0.001$) but gaze to high versus low salience objects was not (high salience: 39%, low salience: 24%, $r = 0.10$, $p = 0.32$). This suggests that high salience objects were much more riveting than low salience objects, and that all faces were attended to similarly whether they faced the observer or were averted.

We began our analyses with very strong a priori hypotheses about gaze in ASD versus TDC participants, based on a significant body of research (Klin et al., 2002; Nakano et al., 2010; Rice et al., 2012). Given that we purposefully calculated our eye tracking variables using Klin and colleagues' methods as a guide, the absence of diagnostic group differences was extremely surprising, and convinced us that the present data warranted a closer look. A number of strategies were used to probe the data and ensure that we did not miss a significant group difference in gaze. Our first follow-up analysis asked whether all children fixated on faces and objects equally quickly from the start of a trial or whether, perhaps, one group was slower to fixate on a certain stimulus type than the other. We hypothesized that the ASD group would fixate on objects more quickly than the TDC group, who would be faster to fixate on faces. As with Total Fixation Duration, however, there was no main effect of diagnosis, $F_{(1,\ 108)} = 0.36$, $p = 0.55$, and no interaction between diagnosis and Type, $F_{(1,\ 108)} = 0.14$, $p = 0.71$,

Table 3 | Gaze predicts face processing skill—entire sample combined.

Variable	Beta	*t*-value	*p*	R^2	ΔR^2
STEP 1					
Age	0.52	6.20	0.000	0.23	0.23
STEP 2					
Gaze to faces	0.27	2.38	0.019	0.27	0.04

Note: Beta is standardized.

Table 4 | Regression with SCQ score predicting face processing skill.

Variable	Beta	*t*-value	*p*	R^2	ΔR^2
STEP 1					
Age	0.48	5.74	0.000	0.23	0.23
STEP 2					
SCQ score	−0.27	−3.41	0.000	0.31	0.08

Note: Beta is standardized.

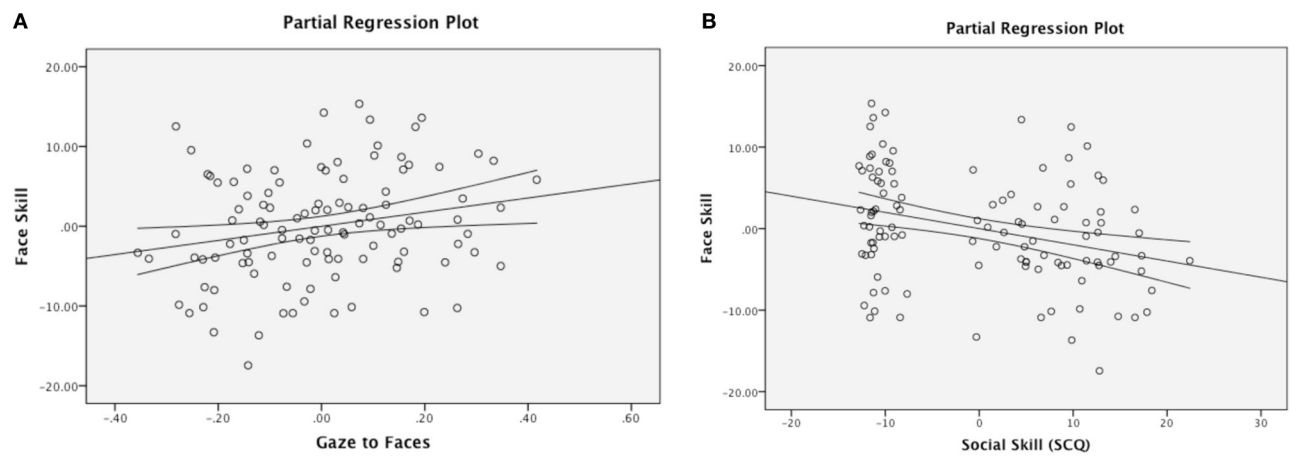

FIGURE 2 | Partial regression plots. Gaze to faces predicting face skill **(A)** and social skill predicting face skill **(B)**, after controlling for the effect of chronological age. (**B**) Additionally illustrates a group difference in social skill.

or diagnosis and Salience, $F_{(1,\ 108)} = 0.41$, $p = 0.52$, or diagnosis, Type, and Salience, $F_{(1,\ 108)} = 0.18$, $p = 0.67$. Next we tested whether the ASD group might study faces and objects differently than the TDC group (e.g., by examining objects in greater detail than faces), which can be indexed by the number of times participants fixate within an AOI. Again, there was no interaction between diagnosis and Type, $F_{(1,\ 108)} = 1.08$, $p = 0.30$, or diagnosis and Salience, $F_{(1,\ 108)} = 2.36$, $p = 0.13$, or diagnosis, Type, and Salience, $F_{(1,\ 108)} = 0.95$, $p = 0.33$. We then tested the hypothesis that children with ASD would visit object AOIs more frequently than face AOIs, and that this pattern would be reversed in the TDC group. Results revealed no interaction between diagnosis and Type, $F_{(1,\ 108)} = 2.20$, $p = 0.14$, or diagnosis and Salience, $F_{(1,\ 108)} = 1.55$, $p = 0.22$, or diagnosis, Type, and Salience, $F_{(1,\ 108)} = 0.10$, $p = 0.75$. We further tested for differences in average visit duration. As with the other variables we explored, there was no interaction between diagnosis and Type, $F_{(1,\ 108)} = 0.09$, $p = 0.76$, or diagnosis and Salience, $F_{(1,\ 108)} = 1.32$, $p = 0.25$, or diagnosis, Type, and Salience, $F_{(1,\ 108)} = 0.44$, $p = 0.51$. Finally, although our sample is matched on chronological age and GCA at the group level, we re-ran the original RMANOVA on total fixation duration, including age and IQ as covariates in the model in addition to diagnosis as a fixed factor. The interaction between diagnosis and Type was still not significant, $F_{(1,\ 106)} = 0.33$, $p = 0.57$, nor was the interaction between diagnosis and Salience, $F_{(1,\ 106)} = 1.59$, $p = 0.21$, or diagnosis, Type, and Salience, $F_{(1,\ 106)} = 0.21$, $p = 0.65$.

First quartile

Long segments of gaze data may obscure meaningful eye movements that occur in the first few seconds of an experiment (Swingley et al., 1998). For this reason, we decided to isolate and examine the first 3.5-s loop of gaze data in each trial. A repeated measures ANOVA on proportion of total fixation duration in the first 3.5 s of each trial revealed no interaction between diagnosis and stimulus Type, $F_{(1,\ 108)} = 1.39$, $p = 0.24$, and no interaction between diagnosis and Salience, $F_{(1,\ 108)} = 0.01$, $p = 0.92$, or diagnosis, Type, and Salience, $F_{(1,\ 108)} = 1.77$, $p = 0.19$.

After exhausting the possibilities, we determined that our original finding, while surprising given the broader literature, was undeniably accurate. As discussed below, we speculate that the object movies in our paradigm may have been too appealing to reveal group differences that other paradigms with more subtle manipulations were able to document.

DISCUSSION

We aimed to answer three questions with this study: First, does visual attention to faces predict face expertise? Confirming our hypothesis, we found that increased gaze to faces relative to objects was a significant positive predictor of children's scores on the *Let's Face It!* Skills Battery. Although the effect is small, it represents an important first step toward understanding the relationship between social attention and one of our most fundamental areas of human expertise. Interestingly, even though the present eye tracking paradigm did not detect diagnostic group (categorical) differences, it was nonetheless sensitive to the dimensional relationship between gaze and face expertise. Future research will need to determine whether this relationship is stronger in different contexts, e.g., when using naturalistic interactive social scenes. More importantly, however, a longitudinal view must be taken. The current study took a cross-sectional approach and does not provide insight into how visual attention to faces contributes to growth in face expertise over the course of development.

Our second hypothesis, that social skill as measured by the SCQ would predict visual attention and face expertise, was partially confirmed. Although children's scores on the SCQ did not predict eye gaze, they did predict face expertise. One obvious limitation of this measure is that the SCQ is not specifically designed to gauge social motivation, which may explain the lack of correlation with visual attention. Future research using an instrument that measures social motivation more directly (such as the Pleasure Scale, Kazdin, 1989, used in ASD populations in Chevallier et al., 2012a,b) may clarify the relationship between motivation and gaze patterns.

Consistent with past work (Klin et al., 2002; Riby and Hancock, 2008; Rice et al., 2012), we asked whether children with ASD would look less at faces during a dynamic video presentation than TDCs. We hypothesized that this effect would be modulated by high versus low salient faces and objects. While there was a significant effect of movie salience, it did not interact with group; children in both diagnostic groups were very drawn to high-salience objects. In fact, participants were so attracted to the high salience stimulus set that there was little overall variance in gaze—most children looked at the high-salience objects the majority of the time. Had children been shown more engaging social stimuli (or less engaging non-social stimuli), diagnostic group differences might have emerged.

In conclusion, our study treated face processing skills as a dimension that spanned both children with ASD and TDC and found that amount of time spent looking at faces during eye tracking predicts face processing skill on an independent measure. This process-based analysis is consistent with a growing emphasis on using dimensional approaches in other areas of mental health research, as captured by the NIMH's new focus on research domain criteria (Insel et al., 2010; Sanislow et al., 2010). Exploring the diverse abilities of children with ASD with an eye toward incremental rather than categorical change has the potential to open new pathways to understanding the heterogeneity characteristic of this uniquely challenging, behaviorally defined disorder. Future research should study face processing longitudinally in large cohorts in order to better test the effect of differential attention to social objects on the development of face processing skills, using dynamic stimuli that span a wide range of salience.

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Continuous cognitive dynamics of the evaluation of trustworthiness in Williams syndrome

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The decision to approach or avoid an unfamiliar person is based in part on one's evaluation of facial expressions. Individuals with Williams syndrome (WS) are characterized in part by an excessive desire to approach people, but they display deficits in identifying facial emotional expressions. Likert-scale ratings are generally used to examine approachability ratings in WS, but these measures only capture an individual's final approach/avoid decision. The present study expands on previous research by utilizing mouse-tracking methodology to visually display the nature of approachability decisions via the motor movement of a computer mouse. We recorded mouse movement trajectories while participants chose to approach or avoid computer-generated faces that varied in terms of trustworthiness. We recruited 30 individuals with WS and 30 chronological age-matched controls (mean age = 20 years). Each participant performed 80 trials (20 trials each of four face types: mildly and extremely trustworthy; mildly and extremely untrustworthy). We found that individuals with WS were significantly more likely than controls to choose to approach untrustworthy faces. In addition, WS participants considered approaching untrustworthy faces significantly more than controls, as evidenced by their larger maximum deviation, before eventually choosing to avoid the face. Both the WS and control participants were able to discriminate between mild and extreme degrees of trustworthiness and were more likely to make correct approachability decisions as they grew older. These findings increase our understanding of the cognitive processing that underlies approachability decisions in individuals with WS.

Keywords: Williams syndrome, hypersociability, mouse-tracking

INTRODUCTION

Evaluations of facial expressions are critical for assessing the approachability of unfamiliar individuals (Winston et al., 2002). Individuals who have Williams syndrome (WS) appear to indiscriminately approach unfamiliar individuals, a feature characterized as hypersociability, and also exhibit deficits in the processing of faces. This combination makes them a critical population for both basic science, where their deficits can inform general theories of person perception and approach-avoid processes, as well as clinical research, as their deficits can leave them vulnerable in some social contexts. The present research seeks to examine the dynamic nature of approachability judgments from facial cues in both individuals with WS and controls.

Individuals with WS display a distinctive and atypical cognitive, behavioral, and neuroanatomical profile. WS has been described as an ideal model in which to investigate the neural substrates of human cognition and behavior. WS is a genetic neurodevelopmental disorder with an estimated prevalence rate of 1 in 7,500 (Stromme et al., 2002), caused by a hemizygous deletion of approximately 26 genes on the long arm of chromosome 7 (Peoples et al., 2000). Individuals with WS typically display a mild to moderate intellectual delay. Relative strengths have been noted in particular aspects of language such as receptive vocabulary and fluency (Don et al., 1999; Mervis and Klein-Tasman, 2000; Robinson et al., 2003; Clahsen et al., 2004; Vicari et al., 2004; see Brock, 2007 for a review), however cross-linguistic studies have shown that the grammatical abilities of individuals with WS are at or below the level of CA- and MA-matched children with intellectual disabilities (other than Down syndrome) as well as MA-matched typically developing (TD) children (Gosch et al., 1994; Volterra et al., 1996; Lukács et al., 2001; Volterra et al., 2003). Individuals with WS have specific deficits in visuospatial skills (Porter and Coltheart, 2006), as well as delays in motor development. Abnormal muscle tone has been documented in individuals with WS, as evidenced by hypotonia in WS children and hypertonia in WS adults (Chapman et al., 1996). Delays in gross and fine motor coordination have also been noted in individuals with WS (Atkinson et al., 1997; Elliott et al., 2006; Hocking et al., 2011). A salient behavioral feature displayed by individuals with WS is their hypersociability, characterized by an excessive desire to meet people, and a lack of stranger anxiety (Bellugi et al., 1999; Frigerio et al., 2006).

The increased sociability in WS has been associated in part with poor emotion identification of facial expressions (Jarvinen-Pasley et al., 2010). TD children as young as 5 years are able to use facial features to make judgments of affective expression and it is these facial features which continue to be used to make rapid judgments of trustworthiness (Cunningham and Odom, 1986; Cowell and Stanney, 2002; Want et al., 2003; Willis and Todorov, 2006). Children with WS show delays in processing happy and sad emotions (Karmiloff-Smith et al., 1995), as well as angry and scared emotions (Porter et al., 2007). Individuals with WS also show deficits matching facial expressions (Levy et al., 2011), focusing attention on angry faces (Santos et al., 2010), and recognizing angry faces (Porter et al., 2010). However, the effect that this perceptual deficit has on social evaluations is not well understood.

The hypersociability displayed by individuals with WS has typically been examined using approachability tasks in which photographs of unfamiliar faces are individually rated on a Likert-scale to determine how approachable they appear. These studies have produced conflicting findings depending on the nature of the task stimuli and whether or not the facial stimuli displayed specific emotions. Individuals with WS rated "positive" (trustworthy and approachable) and "negative" (untrustworthy and unapproachable) faces as more approachable than chronological age-matched controls (Jones et al., 2000; Martens et al., 2009). When viewing faces depicting specific positive and negative emotions, such as happiness, anger, or fear, individuals with WS rated only the happy faces as more approachable (Frigerio et al., 2006). While these behavioral measures help increase our understanding of hypersociability in WS, they do not provide an opportunity to explore the dynamics of cognitive processing as approachability decisions are made.

Cognition is a continuous, dynamic process and static measures which only examine a participant's final choice do not capture this fluidity (Spivey and Dale, 2006). Converging evidence from continuous measures such as eye-tracking suggest that compared to controls, individuals with WS show increased gaze durations when looking at strangers (Mervis et al., 2003), when viewing facial expressions (Porter et al., 2010), and during cognitively challenging tasks (Doherty-Sneddon et al., 2009). Additional research has shown that individuals with WS take longer than TD individuals to disengage from looking at faces than objects (Riby et al., 2011). While these studies highlight abnormalities in perceptual processing associated with WS, they do not help explain WS-related differences in evaluating face stimuli or their hypersociability more generally.

In the current study, we chose to explore hypersociability in WS by examining the dynamic cognitive processing that occurs when individuals are asked to approach or avoid faces of unfamiliar persons via mouse responses. A burgeoning literature suggests that the continuous nature of cognitive processes can be visually displayed via mouse-tracking – the motor movement of a computer mouse as a decision is being made – (Gold and Shadlen, 2001; Shin and Rosenbaum, 2002; Dale et al., 2007). Each decision trial provides continuous data which graphically displays underlying aspects of cognition (Magnuson, 2005). Arm movements that are made when controlling a computer mouse can be adjusted in the process of making a choice and mouse-tracking allows one to visually observe the effects of an alternate choice that may be competing with the correct response. For example, it has been demonstrated that when individuals are shown two objects in opposite corners of a computer screen and are asked to click on the object that is named, the participants will show more attraction (mouse movement) toward the competing object if the object name and the competing name start with the same sound (candle and candy) than with different sounds (candle and jacket) (Spivey et al., 2005). The technique has also been used to investigate gender stereotypes (Freeman and Ambady, 2009), perceptions of race (Wojnowicz et al., 2009; Freeman et al., 2010), and the social categorization of sex (Freeman et al., 2008). This methodology is fairly recent and as such is just beginning to be utilized with individuals who have intellectual disabilities. Its use in this particular study allows us to make more advanced inferences about aspects of cognitive processing that occur as approachability decisions are made in individuals with WS.

MATERIALS AND METHODS

PARTICIPANTS

Thirty individuals with WS (mean age = 20.8 years, range = 8–41 years) and 30 chronological age-matched TD controls (mean age = 20.9 years, range = 8–42) participated in the study. The majority of the data collection from the participants with WS occurred during a WS Syndrome National Convention, with the remaining WS participants recruited locally. The control participants were recruited from the community and from siblings of the WS participants. All of the WS and control participants were Caucasian and right-handed. Appropriate institutional IRB approval was obtained and consent was given by either the participants or their guardians. The parents/guardians all affirmed that their child was comfortable using a computer mouse. Their familiarity with the computer was confirmed by the experimenter, who observed that all participants demonstrated immediate ease at manipulating the computer mouse. The participant demographics are displayed in **Table 1**.

STIMULI

Our stimuli came from a previously published computer-generated face set (Oosterhof and Todorov, 2008), derived using FaceGen Modeller (Inversions, 2007). This face set consists of a series of bald, Caucasian, male faces of European ethnicity. Each face is depicted multiple times with systematic variations that change the perceived approachability/trustworthiness of the face, with inferences of trustworthiness based on similarity to expressions signaling approach or avoidance behavior (Todorov et al.,

Table 1 | Participant demographics.

Characteristic	Overall	WS	Control	*P*-value
N	60	30	30	
Age (years)	20.8 (10.0)	20.8 (10.1)	20.9 (10.0)	1.00
IQ	91.3 (22.2)	73.9 (14.2)	108.8 (13.1)	<0.0001
Female gender, *N* (%)	38 (63%)	21 (70%)	17 (57%)	0.28

Results are presented as mean (SD) except where noted.

2008). We selected 20 faces from the set and used four variations of each, based on their standard deviation (SD) from the average rating: extremely untrustworthy (−4.5 SD); mildly untrustworthy (−1.5 SD); mildly trustworthy (+1.5 SD); and extremely trustworthy (+4.5 SD; see **Figure 1**). These variations resulted in a total of 80 facial stimuli, creating a 2-by-2 design (trustworthiness by extremity). These stimuli were chosen because they lack many irrelevant features of more naturalistic face images (e.g., hair or accessories) that can distract individuals with WS and interfere with their attention to facial expressions (Martens et al., 2009; Capitão et al., 2011).

APPARATUS

The stimuli were shown on a Dell 3700 Vostro laptop computer, with a screen size of 44 cm. The participants sat at a desk approximately 46 cm from the computer screen. The target responses (Green or Red circle) were 6.4 cm in diameter and the face images were 9.6 cm tall and 5.7 cm wide. To get a measure of participants' decision processes across time regarding the trustworthiness of the faces, we tracked their mouse cursor movements as they selected response options in regard to whether they would like to approach or avoid each face. We used the MouseTracker software package (Freeman and Ambady, 2010); available at http://mousetracker.jbfreeman.net, which is a self-contained program which presents and records participants' responses.

PROCEDURE

Participants were presented stimuli in four blocks of 20, with stimuli randomized within each block.[1] On each trial, participants were presented with a single face. Participants were instructed to indicate whether they wished to go up and talk to the individual, by moving the cursor from the bottom center of the screen to select the corresponding circle on the screen (a green circle to approach and a red circle to avoid). A colored green or red circle was placed in the upper left and right corners of the screen, counter balanced across participants (see **Figure 2**). Prior to beginning the first block, participants acquired familiarity with the decision task via a practice block using unrelated stimuli (food).

[1]This design allowed participants who became fatigued to take a break or withdraw from the study without tainting their previously collected data. All four blocks were completed by all control participants and by all but one WS participant.

A face appeared only after participants clicked the mouse on the word "start" to begin each trial. The inter-stimulus interval was 1 s for the red and green circles to reappear and 2 s for the word "start" to appear. Participants were instructed to respond as fast as possible to each stimulus. If participants did not begin moving the mouse within 750 ms of the stimulus onset, or if they did not make a response within 8000 ms, they were encouraged to begin moving more quickly and that trial was not logged. The majority of trials were valid, with 99.5% of control participants' trials and 97.2% of WS participants' trials producing valid responses.

For analysis, some conditions were mirrored such that all trajectories (including incorrect responses) were made to the upper right corner. Consistent with MouseTracker conventions, trajectories were normalized spatially, to a 4-by-3 aspect ratio, and temporally, into 101 time steps. The MouseTracker package computes a summary measure for each trajectory called maximum deviation (MD). MD is a common metric for gauging competition between responses. MD quantifies how far a trajectory deviates toward one option before the participant ultimately settles on the alternative. Thus larger MDs are presumed to indicate greater response competition and more difficulty in making a decision. Following this

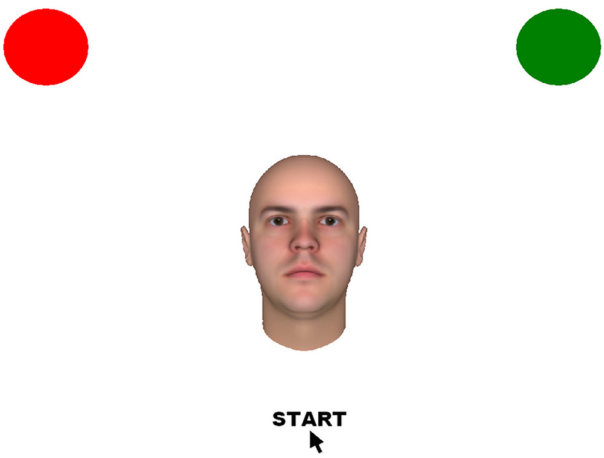

FIGURE 2 | Sample stimuli used in study, in which the participants indicated if they wished to approach or avoid the individual by moving the cursor to either the green (approach) or red (avoid) circle.

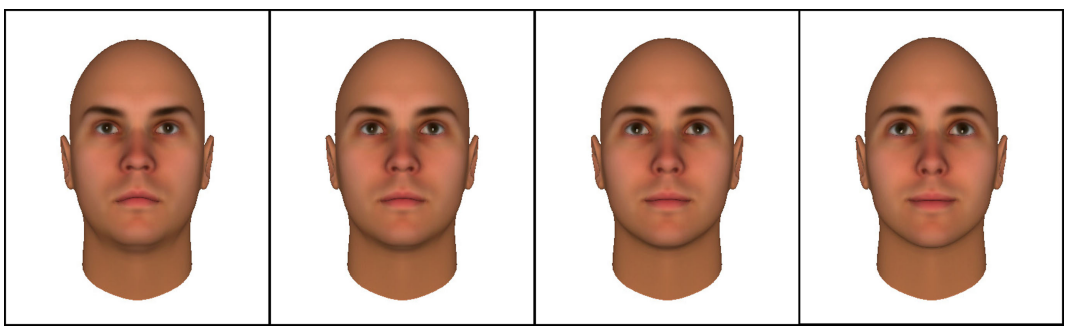

FIGURE 1 | Example of facial stimuli, ranging from "Very untrustworthy" to Very trustworthy (left to right).

task, the individuals were given the Kaufman Brief Intelligence Test, 2nd edition (Kaufman and Kaufman, 2004) in order to gain a measure of their overall ability level.

DATA ANALYSIS

The expected behavior was for participants to choose to approach trustworthy faces and avoid untrustworthy faces. However, the participants did not always respond as expected, and therefore, trials were categorized as "correct" or "incorrect." An analysis of incorrect trials was important, given that the hypersociability aspect of the WS phenotype suggests that there may be differences in the ways that errors are generated. Therefore, analysis investigated factors influencing the frequency with which participants responded in a typical fashion, as well as the MD of both correct and incorrect trials.

Linear and generalized linear mixed models were used to test differences between the WS participants and control participants in the rates of correct responses and the MD (Diggle et al., 2002). This type of analysis allows use of individual trial data, taking into account the fact that trials by the same participant were correlated. A compound-symmetric variance-covariance structure for within-participant correlation was estimated by including a random participant-specific intercept in each model. A logistic mixed model was used to model the frequency of correct responses, using the PROC GLIMMIX procedure in SAS 9.3 with a RANDOM statement, and a linear mixed model was used to model the MDs using the PROC MIXED procedure with a RANDOM statement (SAS Institute, Cary, NC, USA). Since not all trials were completed by all participants, the Kenward–Roger approximation to the degrees of freedom was used to bring Type I error rates to nominal levels (Kenward and Roger, 1997), sometimes resulting in non-integer degrees of freedom.

To test for group differences, all models included the effects of group, face type (four level), and their interaction. Models for MD additionally included an indicator for whether the trial resulted in a correct response, and the interaction of this indicator with group, face type, and their interaction. We determined that the MD of the WS participants was toward the alternate choice 84% of the time (versus toward the outside edge of the computer screen), suggesting that the MD results were not an artifact resulting from errant motor control. To control for potential confounders, adjusted models included the main effects of age, IQ, and reaction time (RT) in milliseconds (ms). Potential effect modification by age was investigated by including the interaction of age and group; this term was not significant in any model and hence was omitted. Gender was not a significant predictor in any models; including it did not impact results and hence was not included in analyses. Orthogonal contrasts were used within the mixed models to estimate adjusted group differences in correct response rates and MD.

RESULTS

REACTION TIMES

The average RT of the WS participants (mean = 1992 ms, SD = 373 ms) was significantly slower than the average RT of the control participants (mean = 1759 ms, SD = 274 ms; $p = 0.008$).

RATES OF CORRECT RESPONSES

An examination of the correct response rates indicates that both the WS and control participants chose to avoid untrustworthy faces and approach trustworthy faces the majority of the time, but the WS participants did so less often than the control participants. Across all trials, the individuals with WS chose the correct response on 69% of trials and the control participants chose the correct response on 93% of trials; both rates were significantly above chance ($p < 0.0001$). Both face type and participant type (WS, control) were significant predictors of correct response ($p < 0.0001$ for both). After adjusting for age, IQ, and RT, there were significant differences in the rates of correctly classified faces between WS and control participants for the extreme faces (**Table 2**). The odds of a WS participant correctly choosing to avoid an extremely untrustworthy face were 0.39 times the odds of a control participant correctly choosing to avoid an extremely untrustworthy face (95% CI: 0.23–0.66, $p = 0.0004$). Similarly, the odds of choosing to approach extremely trustworthy faces was significantly lower for WS participants than for controls (OR = 0.43, 95% CI: 0.27-0.69, $p = 0.006$). There was a smaller but borderline significant difference for mildly trustworthy faces, with WS participants less likely than controls to approach mildly trustworthy faces (OR = 0.64, 95% CI: 0.42–0.98, $p = 0.04$). There were no significant differences between WS and control participants for mildly untrustworthy faces ($p = 0.79$).

Both WS and control participants had higher rates of correct responses for extreme faces as compared to mild faces. For WS participants, the odds of correct classification of an extreme face was 2.2 times the odds for mild faces (95% CI: 1.8–2.6, $p < 0.0001$), with no difference between trustworthy and untrustworthy faces ($p = 0.74$). For control participants,

Table 2 | Correct response rates and adjusted odds ratios comparing WS participants to control participants.

	Correct response rate (%)				
Face type	**WS**	**Control**	**Adjusted odds ratio***	**95% CI**	***P*-value**
Extremely untrustworthy	80	93	0.39	0.23–0.66	0.0004
Mildly untrustworthy	65	69	1.1	0.69–1.6	0.79
Mildly trustworthy	56	72	0.64	0.42–0.98	0.04
Extremely trustworthy	74	90	0.43	0.27–0.69	0.0006

**Adjusted for age, IQ, and reaction time.*

the difference in correct response rates between extreme and mild faces depended on whether the face was trustworthy or untrustworthy. For untrustworthy faces, the odds of a control participant correctly classifying an extreme face was 5.7 times the odds of correctly classifying a mild face (95% CI: 4.0–8.2, $p < 0.0001$), and for trustworthy faces the odds ratio was 3.4 (95% CI: 2.4–4.6, $p < 0.0001$). These two odds ratios were significantly different ($p = 0.03$), showing that it was easier for control participants to differentiate mild versus extreme expressions among the untrustworthy faces, which was not the case for WS participants.

Both age and RT were significantly associated with correct responses. Older participants were more likely to make correct choices, with a 5 year increase associated with 7% higher odds of selecting the expected response ($p = 0.03$). Shorter RTs were associated with a higher rate of correct responses ($p < 0.0001$).

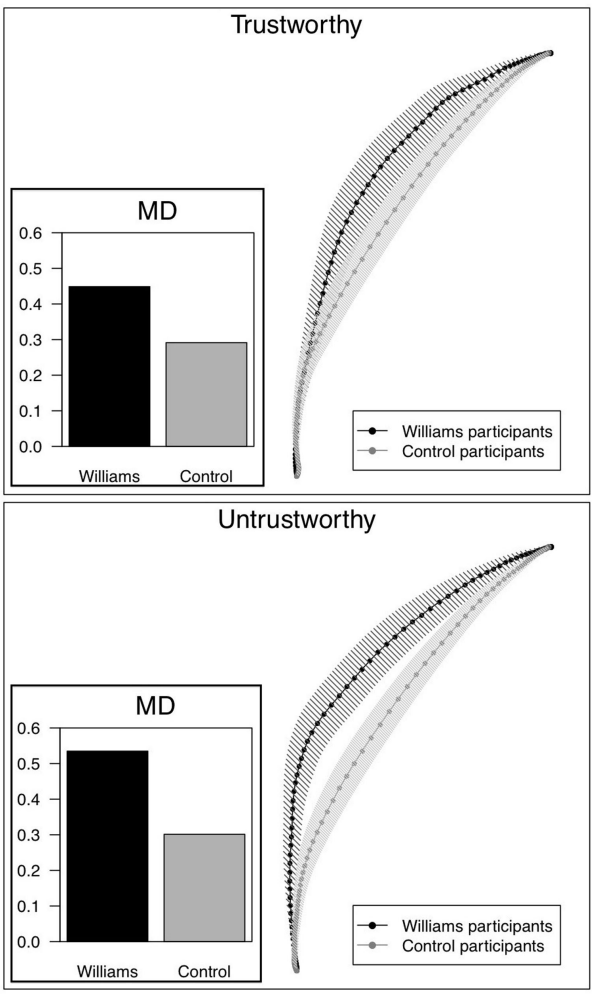

FIGURE 3 | Mean trajectories by face type (trustworthy, untrustworthy) for Williams and control participants, aggregated across extremity of faces and across trials. Shaded region is plus/minus one standard error for each average mouse position. Bar graph shows the adjusted mean maximum deviation for each group of participants.

IQ was not significantly associated with the chance of a correct response.

MAXIMUM DEVIATION FOR CORRECT TRIALS

For faces where participants did not make an error (75% of trials overall), WS participants had larger MD on average than control participants, across all face types. **Table 3** shows the average MD by participant group and trustworthiness, adjusting for age, IQ, and RT. There was not a significant effect of extremity of faces. Differences in MD between WS and control participants were more pronounced for untrustworthy faces (see **Figure 3**). WS participants considered approaching untrustworthy faces significantly more than controls, as shown by a significantly larger MD for these faces (0.53 vs. 0.30, $p = 0.005$). WS participants also considered avoiding trustworthy faces more than control participants, though the difference in MD was of borderline significance (0.45 vs. 0.29, $p = 0.06$). For WS participants, the tendency to consider approaching the untrustworthy faces was larger than the tendency to avoid the trustworthy face, as evidenced by a significant difference in MD (0.53 vs. 0.45, $p = 0.0001$); this pattern was not seen in control participants (MD 0.30 vs. 0.29, $p = 0.61$). In other words, individuals with WS were more likely than controls to initially deviate toward untrustworthy faces. In WS participants, the bias to approach untrustworthy faces was larger than the bias to avoid trustworthy faces. No such differences were observed in control participants.

MAXIMUM DEVIATION FOR INCORRECT TRIALS

For faces where participants did make errors (25% of trials overall), WS participants considered approaching trustworthy faces that they ultimately chose to avoid significantly more than controls, as shown by a larger MD (0.50 vs. 0.27, $p = 0.01$), adjusting for age, IQ, and RT (see **Table 3**). However, there was no significant difference between WS and control participants in their tendency to avoid untrustworthy faces that they ultimately chose to approach (MD 0.38 vs. 0.32, $p = 0.50$). For WS participants, the tendency toward approaching a trustworthy face that was ultimately avoided was larger than the tendency to avoid the untrustworthy face that was ultimately approached, as evidenced by a significant difference in MD (0.50 vs. 0.38, $p = 0.001$); this pattern was not seen in control participants (MD 0.27 vs. 0.32, $p = 0.61$). That is to say, WS individuals were more likely than controls to consider approaching trustworthy faces. There was no difference between WS and control participants in the deviation toward avoiding untrustworthy faces. As seen in the correct trials, the approach bias was larger than the avoid bias for WS participants but not for controls.

DISCUSSION

Individuals with WS display an increased tendency to approach strangers, which makes them vulnerable to exploitation. Hypersociability in WS has typically been examined using behavioral methodologies that incorporate stimuli with varied facial emotional expressions. However, distinguishing facial emotional expression is just one facet of social judgment decision-making (Winston et al., 2002). An individual also needs to decide how trustworthy a person appears before deciding if he/she wants to approach or avoid them. The present study aims to investigate the

Table 3 | Maximum deviation for WS and control participants, for correct and incorrect trials. Adjusted for age, IQ, and reaction time.

Trial type	Face type	Participant response	Deviation toward	Williams Mean (SE)	Control Mean (SE)	Difference Mean (SE)	*P*-value
Correct	Untrustworthy	Avoid	Approach	0.53 (0.05)	0.30 (0.05)	0.23 (0.08)	0.005
	Trustworthy	Approach	Avoid	0.45 (0.05)	0.29 (0.05)	0.16 (0.08)	0.06
Incorrect	Untrustworthy	Approach	Avoid	0.38 (0.05)	0.32 (0.06)	0.06 (0.09)	0.50
	Trustworthy	Avoid	Approach	0.50 (0.05)	0.27 (0.06)	0.23 (0.09)	0.01

dynamic cognition processing that occurs when individuals with WS are making approach/avoid decisions in response to faces of unfamiliar people who vary in degree of trustworthiness.

An examination of the error rates demonstrated that the individuals with WS were more likely than controls to choose to approach the untrustworthy faces. Furthermore, the real-time motor trajectories revealed that the WS participants considered approaching untrustworthy faces significantly more than controls, as evidenced by their larger MD, before eventually choosing to avoid the face. The control participants appeared to be more definitive in their choice to avoid and did not appear to deviate toward approaching the untrustworthy face as much as the WS participants. These results support evidence indicating that individuals with WS show an approach bias to some negative facial expressions (Bellugi et al., 1999; Jones et al., 2000; Martens et al., 2009; Fishman et al., 2011).

The current findings also support increasing evidence from structural and functional neuroimaging studies that have examined the neural basis of hypersociability in WS. Most imaging studies have focused on the amygdala, which has been shown to be a principal structure in the evaluation of fear (Adolphs, 1995, 2003; Phelps, 2006) and in making social judgments of approachability and trustworthiness (Adolphs et al., 1998; Winston et al., 2002). Increased amygdala volume in individuals with WS has been associated with increased approachability ratings for unapproachable faces (Martens et al., 2009), while functional imaging studies have demonstrated that the amygdala in WS shows decreased reactivity to negative facial expressions (Meyer-Lindenberg et al., 2005; Haas et al., 2009; Plesa-Skwerer et al., 2009).

We also found individuals with WS were more likely than controls to choose to avoid an extremely trustworthy face, and to a lesser degree, a mildly trustworthy face. These results may be associated with the fact that the facial expression on the trustworthy faces showed no teeth and no definitive smile, and therefore may have appeared more neutral than happy (see **Figure 1D**). Previous results have shown that individuals with WS rate neutral faces as "medium approachable" (Capitão et al., 2011). These findings might also reflect the previous finding that individuals with WS have more difficulty than controls in interpreting facial expressions (Gagliardi et al., 2003; Plesa-Skwerer et al., 2006; Porter et al., 2007; Capitão et al., 2011), and have atypical eye scanpath patterns when viewing both positive and negative facial expressions (Porter et al., 2010).

The current findings are the first to suggest that individuals with WS can discriminate mild vs. extreme degrees of trustworthiness, albeit not as accurately as controls. The participants with WS made more errors on the mild than extreme faces for both the untrustworthy and trustworthy faces. The difficulty of discriminating degree of trustworthiness may be associated with the previous finding that individuals with WS make more errors than control participants when labeling facial expressions (Gagliardi et al., 2003; Plesa-Skwerer et al., 2006; Porter et al., 2007; Jarvinen-Pasley et al., 2010; Capitão et al., 2011).

Importantly, our findings also demonstrate that older individuals with WS, like the older control participants, are more likely to make correct approachability decisions than younger participants. There has been little examination of the development of hypersociability in WS. Martens et al. (2009) found that adults with WS were more likely to use typical facial features to determine approachability than children. Additional research is needed in order to investigate the development of hypersociability in WS more fully.

The data appear to contradict previous studies that have demonstrated that individuals with WS do not show an attention bias to angry faces (Dodd and Porter, 2010) and they rate faces depicting negative emotions, such as anger, disgust, and fear, as unapproachable (Frigerio et al., 2006). The reason for the conflicting evidence may depend in part on the nature of the task stimuli utilized in the various studies. The studies conducted by Bellugi et al. (1999), Fishman et al. (2011), Jones et al. (2000), and Martens et al. (2009) used facial stimuli that had been rated by the normative sample as untrustworthy and unapproachable (Adolphs et al., 1998). In contrast, the studies by Dodd and Porter (2010) and Frigerio et al. (2006) utilized facial stimuli that depicted angry and fearful faces. So while there is evidence that individuals with WS appear to be able to distinguish anger and fear, they may have more difficulty evaluating the approachability of faces that vary in degree of trustworthiness. This conclusion is further supported by evidence that individuals with WS have difficulty inferring complex emotions, including "don't trust," (Riby and Back, 2010).

We recognize that this mouse-tracking task requires fine motor coordination and visual control of spatially directed hand movements, skills which are difficult for many individuals with WS (Atkinson et al., 1997; Elliott et al., 2006; Hocking et al., 2011). Elliott and colleagues evaluated mouse cursor movements in four individuals with WS and found that they demonstrated slower RTs and had more errors than adults with other types of developmental disabilities. Slower RTs were also observed in adults with WS who used a stylus on a touchscreen to draw a horizontal line between circles that varied in size and in distance from one another (Hocking et al., 2011). In addition, individuals with WS have been shown to have difficulty posting a card through slots with various orientations (Atkinson et al., 1997). In the card post task, individuals with

WS displayed awkward arm and hand postures as they attempted to rotate the card to match the slot's orientation. However, it seems unlikely that the spatial nature of our task was responsible for the pattern of responses that we obtained. We controlled for RT in our statistical analyses and the experiment was designed so that participants could click anywhere on the response circle (green to approach or red to avoid), so they did not have to click directly on a small target. Furthermore, the mouse-tracking task, although still requiring visuomotor control, did not require hand or arm rotations and the surface of the table might have helped stabilize their arm motor movements.

At this point we do not have data to measure the reliability of approachability ratings using a mouse-tracking paradigm compared to traditional Likert-scale ratings, but this is an area we plan to investigate in future studies. In addition, our MD findings are limited in that the mouse-tracking software does not afford automated time-course analyses in order to more closely examine the pattern of the trajectory. Now that mouse-tracking software has been utilized in WS using automated metrics, it would be interesting for future studies to expand the current findings by conducting time series analyses of the trajectories. It would also be important to evaluate the ecological validity of the mouse-tracking task using complementary *in vivo* studies of sociability. Such studies might include showing faces that vary in degrees of trustworthiness on two video screens, and asking individuals with WS to walk toward the video screen of the person that they wish to approach. Showing physical movement toward a target would be a logical extension of the trajectory of a computer mouse.

Although the outgoing and friendly nature of individuals with WS makes them endearing, parents are well aware that this aspect of their personality makes them extremely vulnerable to exploitation. We are the first to use mouse-tracking methodology to examine hypersociability in WS and believe this that methodology increases our understanding of the continuous cognitive processes that may underlie hypersociability in WS. Mouse-tracking trajectory data have been validated using simulated trajectories and other RT data (Freeman and Ambady, 2010). Rather than relying on Likert-style tasks which rely only on end point decisions, mouse-tracking data allow us to view the dynamics of approachability decisions and to compare these dynamics between individuals with WS and controls. Mouse-tracking trajectories which depict a fairly straight trajectory between the starting point (i.e., viewing an untrustworthy face) and the final choice (choosing to avoid) suggest that the decision is fairly firm and the person is not strongly considering approaching the face. On the other hand, mouse-tracking trajectories which deviate a great deal toward approaching an untrustworthy face before finally deciding to avoid the face inform us about the dynamic nature of some approachability decisions and help characterize the hypersociability noted in WS.

These findings may also assist in the development of interventions that can improve the emotion processing skills of individuals with WS. For example, individuals with WS could be taught to discriminate how facial features change from trustworthy to untrustworthy (i.e., the inner portion of the eyebrows lower and the corners of the mouth turn down). Mouse-tracking could then be used to determine if this type of intervention training influences mouse trajectories as decisions of approachability are made. Research suggests that interventions can be successful in helping individuals improve their recognition of facial expressions (Dadds et al., 2006). Individuals who are taught to accurately detect and identify facial expressions demonstrate increased positive social interactions and decrease self-reported feelings of anxiety (Izard et al., 2001). There is increasing evidence that deficits in emotion perception can be remediated among individuals with developmental disabilities. Remediation in correctly perceiving emotions from facial cues has resulted in improved emotion perception in adults with intellectual disabilities. Importantly, these findings have generalized from viewing photographs to viewing videotaped role plays and have persisted for at least nine months (McAlpine et al., 1992). Similarly, training individuals with autism to correctly process facial expressions resulted in brain activation changes in regions underlying facial processing (Bolte et al., 2006). Behavioral outcome measures have been used to verify the benefits of emotion processing training (Radice-Neumann et al., 2009) and therefore mouse-tracking paradigms may be beneficial in evaluating the effectiveness of emotion processing interventions and their effects on hypersociability in individuals with WS.

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Sensitivity of the autonomic nervous system to visual and auditory affect across social and non-social domains in Williams syndrome

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Although individuals with Williams syndrome (WS) typically demonstrate an increased appetitive social drive, their social profile is characterized by dissociations, including socially fearless behavior coupled with anxiousness, and distinct patterns of "peaks and valleys" of ability. The aim of this study was to compare the processing of social and non-social visually and aurally presented affective stimuli, at the levels of behavior and autonomic nervous system (ANS) responsivity, in individuals with WS contrasted with a typically developing (TD) group, with the view of elucidating the highly sociable and emotionally sensitive predisposition noted in WS. Behavioral findings supported previous studies of enhanced competence in processing social over non-social stimuli by individuals with WS; however, the patterns of ANS functioning underlying the behavioral performance revealed a surprising profile previously undocumented in WS. Specifically, increased heart rate (HR) reactivity, and a failure for electrodermal activity to habituate were found in individuals with WS contrasted with the TD group, predominantly in response to visual social affective stimuli. Within the auditory domain, greater arousal linked to variation in heart beat period was observed in relation to music stimuli in individuals with WS. Taken together, the findings suggest that the pattern of ANS response in WS is more complex than previously noted, with increased arousal to face and music stimuli potentially underpinning the heightened behavioral emotionality to such stimuli. The lack of habituation may underlie the increased affiliation and attraction to faces characterizing individuals with WS. Future research directions are suggested.

Keywords: williams syndrome, affect, electrodermal activity, heart rate, facial expression, autonomic nervous system, psychophysiology

INTRODUCTION

Understanding the underpinnings of human social behavior is of relevance to both typical development as well as neurodevelopmental disorders. Within this realm, the unusual social phenotype associated with Williams syndrome (WS) has brought this neurogenetic condition to the forefront of interest within the neuroscience community. Specifically, WS, caused by a contiguous deletion of 25–30 genes on chromosome 7q11.23 (Ewart et al., 1993; Korenberg et al., 2000), combined with a distinctive social profile, holds promise for discovering linkages between neurobiological, physiological, behavioral, and genetic systems that provide meaning to human social interaction. Individuals with WS demonstrate an unusually positive expression of affect, abnormally expressive language in narratives, increased attraction to and engagement with strangers, a propensity to direct eye contact, a relative strength in identifying and remembering faces, increased empathy, and an increased emotional reactivity to music combined with intriguing dissociations, which include overly friendly behavior with a difficulty in making friends, social fearlessness coupled with anxiety, and abundant positive affect with maladaptive behaviors (see Dykens, 2003; Levitin et al., 2004; Meyer-Lindenberg et al., 2006; Järvinen-Pasley et al., 2008; Martens et al., 2008; Riby and Porter, 2010; for reviews). Perhaps not surprisingly, in general terms, WS is associated with more competent processing of social as compared to non-social information (e.g., Martens et al., 2008), a remark that we recently extended into the realm of emotion processing of faces vs. non-social images (Järvinen-Pasley et al., 2010a).

Although the social affective characteristics have variably been described in WS for a decade, specifically the role of the underlying autonomic nervous system (ANS) function in the fascinating social phenotype remains largely unknown. This question is of significance for several reasons. First, individuals with WS have been described as demonstrating heightened emotional reactivity at the behavioral level (e.g., Tager-Flusberg and Sullivan, 2000; Levitin et al., 2004), and it is currently not understood whether this unusual sensitivity may play a role in regulating the reward

value of social encounters for individuals with WS. Second, the examination of patterns of ANS sensitivity of individuals with WS to affective social and non-social stimuli within both visual and auditory in modalities may provide some clues regarding the nature of the diagnostically significant anxiety associated with the syndrome. Thus, the social behavior associated with WS comprises a panoply of distinct socially positive and maladaptive behaviors implicating the dysfunction of multiple neural circuits. As both electrodermal activity (EDA) and heart rate (HR) are amygdala-associated non-invasive and robust measures of autonomic function indexing sensitivity to social affective information at physiological levels (LeDoux, 2000; Adolphs, 2001; Laine et al., 2009), they provide useful tools for elucidating the underpinnings of the social-emotional phenotype associated with WS. Moreover, the physiological processes indexed by electrodermal responses and HR are regulated by the hypothalamic-pituitary axis (HPA) implicated in a variety of social behaviors across species (Pfaff, 1999; Goodson, 2005). More broadly, understanding the role of autonomic function to social tendencies is also of interest from standpoint of individual differences research, as the extraverted and introverted personality profiles have also been linked to individual differences in ANS functioning. Specifically, differences in arousal between extraverts and introverts have been linked to emotional experience and social behavior (Eysenck, 1967, 1994, 1997). Whereas extraverts seek more frequent and intense stimulation (e.g., social interaction) to raise their inherently low level of arousal to an optimal level, introverts tend to exhibit the opposite pattern. Thus, compared to extraverts, introverts are thought to be inherently more aroused and arousable (Stelmack, 1990; Smith, 1994); exhibit higher HR reactivity (Smith et al., 1995); higher skin conductance levels (SCL; Smith et al., 1986); greater phasic skin conductance response (SCR; Smith et al., 1990); and slower electrodermal habituation (Smith et al., 1995). Although some aspects of this theory have been questioned (see e.g., Beauducel et al., 2006, for a discussion), it is nevertheless of interest to explore how the WS social profile of anxiousness coupled with hypersociability and its ANS correlates fit in with this line of research, as some behavioral features resemble typical extraverted behavior. WS provides a special window into the underpinnings of social information processing due to it representing atypical genetic expression, linked to increased social and emotional behavior.

A handful of previous studies have explored electrodermal and/or HR activity in WS within the visual domain. In one study, Plesa Skwerer et al. (2009) presented individuals with WS, chronological age (CA)-matched typically developing (TD) individuals, and those with mental disabilities matched for language abilities, with dynamic facial expressions anger, disgust, fear, happiness, sadness, surprise, and neutral emotion, while SCR and HR were recorded. Emotionally neutral nature videos were also presented. The results indicated that relative to both control groups, WS was associated with hypoarousal in response to face stimuli, and these participants also showed more pronounced HR deceleration, interpreted as indexing heightened interest in such stimuli. In another study, Doherty-Sneddon et al. (2009) assessed changes in SCR while individuals with WS and CA-matched TD controls completed arithmetic tasks varying in both difficulty and the extent of eye contact with the experimenter. In another task, the extent of gaze aversion in relation to cognitive load was assessed. The results showed that while WS was associated with general hypoarousal and reduced gaze aversion, similar to the TD controls, their arousal level increased in response to face stimuli. The authors suggested that lower than typical arousal level may enable individuals with WS to hold face and eye gaze for prolonged periods of time, which may underlie their aberrant face and eye gaze processing strategies, and ultimately, some social features (see, e.g., Riby and Hancock, 2008, 2009). Plesa Skwerer et al. (2011) recently tested ANS responsivity as reflected in pupil dilation in individuals with WS contrasted with CA- and MA-matched control groups in response to viewing images with social vs. non-social content. The results showed that although all groups showed greater arousal to the social as compared to the non-social images, the WS group displayed decreased pupil dilation to faces expressing negative affect relative to the controls. It is also noteworthy that overall, WS was associated with decreased pupil dilation to the social stimuli, suggesting reduced arousal to social stimuli relative to the control groups. Finally, Riby et al. (2012) examined SCL reactivity in response to live and video-mediated displays of happy, sad, and neutral affect in individuals with WS, TD, and autism. The results showed that only live faces increased the level of arousal for those with WS and TD. Participants with WS displayed lower SCL as compared to the TD group, which the authors interpreted as suggesting hypoarousal in this group.

Taken together, the findings described above raise several questions about the role of ANS functioning within the WS social phenotype. The studies of Plesa Skwerer et al. (2009), Doherty-Sneddon et al. (2009), and Riby et al. (2012) will be considered here as they are of specific relevance to the current study due to them involving EDA and/or HR measures. In particular, the discrepant finding of hyporesponsivity to emotional face stimuli in Plesa Skwerer et al.'s (2009) study and the typical increase in arousal in response to faces in Doherty-Sneddon et al.'s (2009) and Riby et al.'s (2012) studies warrants further research. It is possible that the different nature of the paradigms used contributes to this seeming contradiction: namely, while the studies of Doherty-Sneddon et al. and Riby et al. involved a naturalistic social context with live face stimuli, Plesa Skwerer et al. (2009) used computer-delivered facial displays of affect. Differences in methodologies employed between the two studies may further account for some of the inconsistencies. To address these gaps, the current study will involve two analogous paradigms across the visual and auditory modalities, contrasting the processing of social (face/voice) with similar non-social (image of an object or scene/music) stimuli matched for emotion. The non-social contrast condition will allow us to determine the extent to which social stimuli are special for individuals with WS. Further, extending this line of research into the domain of auditory processing is important, as affective expressions typically are multimodal, and critical social information is provided both by a face and a voice. Albeit scarce, there is evidence of aberrant behavioral and neurobiological organization of socially relevant auditory processing in WS (see, e.g., Järvinen-Pasley et al., 2010b). It is noteworthy that in general, significantly less is known about the neural processing of aurally presented, as compared with visually presented affect (Adolphs, 2002), although both facial expressions and affective vocalizations comprise the

two most frequently employed channels of communicating emotion in social interactions. Thus, a systematic study in which the same participants complete analogous visual and auditory tasks as is proposed here will elucidate such processes.

Given that the current paradigms were more similar in nature (i.e., not representing naturalistic social situations) to that of Plesa Skwerer et al. (2009) as compared to those of Doherty-Sneddon et al. (2009) and Riby et al. (2012), we hypothesized that relative to TD participants, individuals with WS would exhibit attenuated EDA and greater HR deceleration in response to affective social stimuli, while the opposite pattern would be predicted for the non-social stimuli (e.g., face vs. non-social images; human vocalizations vs. music). The opposite profiles across the social and non-social domains were predicted for the TD group.

EXPERIMENT 1: FACES vs. SCENES: ANS SENSITIVITY TO VISUAL SOCIAL AND NON-SOCIAL AFFECTIVE STIMULI

MATERIAL AND METHODS

Participants

Twenty-two individuals with WS (eight males) were recruited through a multicenter program based at the Salk Institute. For all participants, genetic diagnosis of WS was established using fluorescence *in situ* hybridization (FISH) probes for elastin (ELN), a gene invariably associated with the WS microdeletion (Ewart et al., 1993; Korenberg et al., 2000). In addition, all participants exhibited the medical and clinical features of the WS phenotype, including cognitive, behavioral, and physical features (Bellugi et al., 2000). Twenty-seven TD individuals (11 males) were recruited as controls; however, the data of four participants were excluded from the analyses due to perseveration, specifically, they responded to all non-social stimuli as "neutral." This resulted in a final sample of 23 TD individuals (nine males) in the behavioral analysis. In subsequent psychophysiology analyses (different recordings than the behavioral data), identification accuracy was a factor controlled in our modeling approach, hence, this sample contained 20 individuals with WS (eight males; mean age = 27.57, SD = 7.70; the data from two participants with WS were excluded due to excessive recording artifact) and 27 TD participants (11 males; mean age = 21.40, SD = 4.32). The participants were screened for the level of education, and those with more than 2 years of college-level education were excluded from this study. Each participant was screened for current and past psychiatric and/or neurological problems, and only those deemed clinically asymptomatic were included in the study. All participants were of the same cultural background, i.e., American.

The participants' cognitive functioning was assessed using the Wechsler Intelligence Scale. Participants under 16 years of age were administered the Wechsler Intelligence Scale for Children Third Edition (WISC-III; Wechsler, 1991), and those above 16 years of age were administered either the Wechsler Adult Intelligence Scale Third Edition (WAIS-III; Wechsler, 1997) or the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Participants were also administered the Benton Test of Facial Recognition (Benton et al., 1983), a perceptual face discrimination task. In addition, all participants were native English speakers, and gave written informed consent before participation. Written informed assent was also obtained from participants' parents, guardians, or conservators. All experimental procedures complied with the standards of the Institutional Review Board at the Salk Institute for Biological Studies.

Table 1 shows the demographic characteristics of the final sample of participants with WS and TD. The participants differed in terms of CA [$t(43) = 2.93$, $p = 0.005$] with the WS group being older than the TD group. While the WS and TD groups did not differ significantly on the basis of the Benton Test standardized scores [$t(43) = -1.48$, $p = 0.15$], expectedly, the TD group scored significantly higher on VIQ, PIQ, and FSIQ (all $p < 0.001$). Pearson correlations exploring the potential contributions of CA, Benton Test standardized scores, VIQ, PIQ, and FSIQ to task performance showed that for those with WS, VIQ correlated positively with the identification of facial emotion [$r\ (18) = 0.59$, $p = 0.009$], while all other correlations failed to reach significance (all $p > 0.11$). No significant associations emerged for the TD group (all $p > 0.12$).

Stimuli

For the social condition, the visual stimuli comprised 24 standardized images of facial expression taken from the Mac Brain/NimStim Face Stimulus Set[1] (Tottenham et al., 2009). There were eight faces (four male and four female) for each of three emotions (happy, fearful, and neutral). The faces with the highest validation ratings were selected. For the non-social condition, 24 different images from the International Affective Picture System (IAPS; Lang et al., 1995) depicted affective scenes and objects; there were eight pictures for each of three emotions (happy, fearful, and neutral). None of the non-social images contained human faces. The happy IAPS stimuli included the following image numbers: 1920, 5200, 5480, 5760, 5910, 7260, 7330, and 8502. The fearful IAPS stimuli included the following image numbers: 1120, 1200, 1525, 1930, 5971, 6230, 9480, and 9600. The neutral IAPS stimuli included the following image numbers: 7006, 7010, 7035, 7080, 7090, 7150, 7170, and 7235. One hundred college students (half female) have rated each of the images in the IAPS set for valence, arousal, and dominance; thus, norms are available for each image in the IAPS manual (Lang et al., 1995). Consistent with Baumgartner et al.'s (2006) study, and our previous study (Järvinen-Pasley et al., 2010a), a pilot study to facilitate selecting the visual non-social stimuli was carried out. Forty typical adults, who did not participate in the present experiments, identified the valence, and used a nine-point Likert-style scale to rate the intensity of a large set of IAPS stimuli. The piloting phase included 45 non-social images (15 images per emotion). The images that most reliably conveyed the intended emotion and had the greatest intensity became the test stimuli (except in the case of neutral affect, for which the images associated with the lowest intensity were selected). Overall, the valence and arousal ratings from our pilot study were similar to those that Lang et al. (1995) found in adults. Given that the IAPS stimuli have a relatively limited number of non-aversive non-social images that do not contain human faces, it was necessary to include images containing animals within the non-social category. The rationale for including NimStim face stimuli and IAPS images as stimuli was that, it is well

[1] www.macbrain.org

Table 1 | Mean characteristics of the participant groups (SD; range in parentheses) in Experiment 1.

	CA (SD; range)	VIQ (SD; range)	PIQ (SD; range)	FSIQ (SD; range)	Benton SS (SD; range)
WS ($n = 22$)	27.3 (8.2; 13–46)	71 (8.3; 55–86)	63 (9.3; 53–72)	66 (7.5; 51–84)	93 (19.1; 55–129)
TD ($n = 23$)	21.5 (4.6; 18–41)	112 (9.76; 89–129)	113 (9.2; 89–127)	114 (7.91; 99–126)	100 (13.4; 74–130)

established that these two classes of affective stimuli elicit differential neural responses (e.g., Meyer-Lindenberg et al., 2005), and thus differences in autonomic responsivity were also expected. Both the face and non-social stimuli were standardized for brightness and contrast using Matlab (MathWorks, Inc.).

Procedure

The experiment was conducted in a quiet room. Participants sat in a comfortable chair in a well-lit room, 130 cm away from a TFT monitor (screen resolution of 1680×1050 pixels). The experiment had two parts: a passive version, which was always administered first (for psychophysiological measurement), and an active task, during which participants made affect identification judgments. The stimuli were presented on a desktop computer running Matlab (Mathworks, Inc.), which delivered a digital pulse embedded in the recording at the onset of each stimulus. To measure physiological responses, after a fixation cross for 1000 ms, each stimulus was presented for 5000 ms, separated by an interstimulus interval (ISI) of 9000 ms (blank screen) to allow enough time for autonomic activity to return to near baseline levels. The stimuli were randomized with respect to both stimulus type (social/non-social) and affect valence (fearful/happy/neutral), and preceded by a blinking fixation cross. Participants were told that pictures of faces and scenes/objects/animals would appear on the screen in a random order. For the passive task, participants were only instructed to look at the pictures carefully, while remaining as quiet and still as possible. For the active task, participants were shown the same stimuli again with a briefer exposure than in the passive task (2000 ms), and asked to identify the emotion shown by the stimuli. Prior to the onset of the active task, the experimenter then showed the response screen to the participant, which listed the three possible emotions to ensure that the participant understood each of the emotion options (scary/scared, happy, and "no emotion" as a label for neutral). The participants responded verbally, and the experimenter operated the computer keyboard on the participant's behalf. After each behavioral trial, participants were asked to identify the gender of the faces, and the scene/object name to ensure attention was maintained throughout the task. No group differences were observed in post-trial questions ($p = 0.96$).

ANS measures and statistical analyses

For both experiments 1 and 2, EDA and electrocardiogram (ECG) measures were recorded during the passive stages of the experiments using BioPac MP150 Psychophysiological Monitoring System (BioPac systems, Inc., Santa Barbara, CA, USA) at a sampling rate of 1000 Hz. Ag/AgCl electrodes where applied to the skin with an isotonic NaCl electrolyte gel placed on the index and middle distal phalanges of the participant's non-dominant hand to record EDA. ECG was recorded with two electrodes, one attached to the right forearm, and the other attached to the left ankle, below the true ankle joint, located on the calcaneus. Recording sessions for each modality were preceded by a 5-min period of rest for the participant, during which baseline measurements were established. During the experiment, stimulus onsets were marked with trigger codes, embedded into the recordings.

All ANS measures were analyzed 7 s subsequent to stimulus presentation on a trial-by-trial basis, in comparison to a 3 s prestimulus baseline. All measured signals (EDA and ECG) were qualitatively inspected for the presence of artifacts. All trials containing outliers, which exceeded 2.5 SDs above or below the mean, were removed from analyses. Mean HR and inter-beat interval (IBI) measures were calculated from the raw ECG signal. After defining the R peak of the heart beat cycle, we calculated the mean and standard deviation of the inter-beat interval (sdIBI) to assess variation in heartbeats for each condition of the experiment. Quantification of the mean IBI is used in conjunction with mean HR since it is a more sensitive and direct measure of parasympathetic and sympathetic system activation (Bernston et al., 1995). Measurement of the sdIBI mirrors the more commonly seen calculation of root mean square of successive differences in heart beat intervals (RMSSD), and thus high frequency heart rate variability (HRV) information corresponding to vagal influence and parasympathetic activity (Bernston et al., 2005; Mendes, 2009). The standard deviation of IBI was chosen as an indirect time-domain measure of HRV due to the randomized and, relatively, quick presentation of stimuli.

All psychophysiology data were analyzed using R (R Development Core Team, 2008), and the R package *nlme* (Pinheiro et al., 2012). A linear mixed-effects model approach was used to assess mean tonic EDA, mean HR, sdIBI, and mean IBI measures taking into account random effects due to individual differences between-participants, autocorrelations between subsequent trials measurements, and possible covariates (age and accuracy on the behavioral task). Fixed effects in our models included group (WS/TD), condition (social/non-social), emotion (fearful/happy/neutral or sad), and the trial number (48 levels). For clarity, we report the F and p values of the Type III Sum of Squares tests of fixed effects from our models. We do not report degrees of freedom in our comparisons since these calculations in linear mixed-effects models are simply approximations. All pair-wise comparisons were Bonferroni corrected. The normality and homogeneity assumption for the linear mixed-effects models was assessed by examination of the distribution of residuals.

RESULTS

Behavioral affect identification

Figure 1 displays the percentage of correct identifications within each affect category (fearful/happy/neutral) across the social and non-social stimulus conditions in Experiment 1 for participants with WS and TD (total number of trials per affect category = 8).

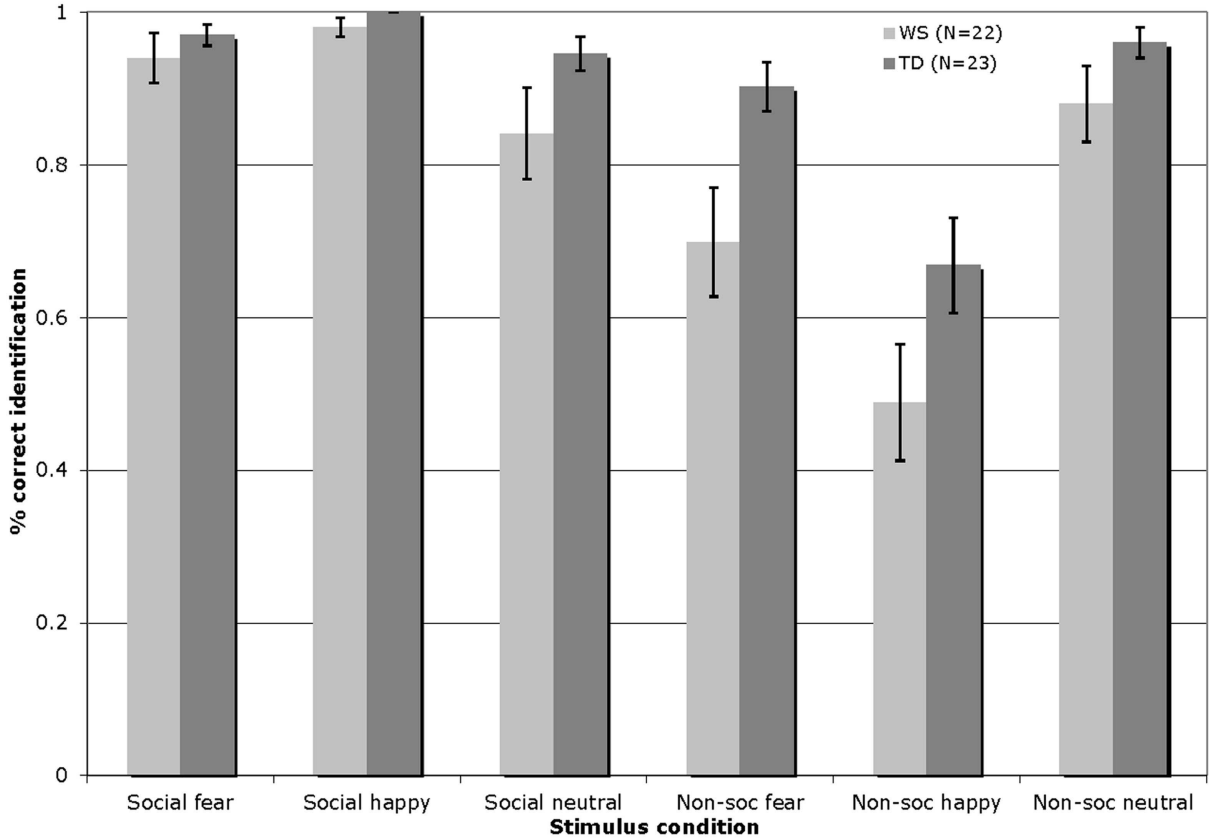

FIGURE 1 | Accuracy of visual affect identification for individuals with WS and TD, across the happy, fearful, and neutral categories for both social and non-social stimuli in Experiment 1. (Total number of trials per affect category = 8; Error bars represent ± 1 standard error mean, SEM).

The visual affect identification data were analyzed by a $2 \times 3 \times 2$ repeated-measures ANOVA, with the condition (social/non-social) and emotion (fearful/happy/neutral) entered as within-participants factors, and group (WS/TD) as a between-participants factor. This analysis revealed a significant main effect of condition [$F(1, 43) = 53.52$, $p < 0.001$], reflecting higher levels of performance overall with the social stimuli; a significant main effect of emotion [$F(2, 86) = 7.49$, $p = 0.001$], with higher levels of identification of the fearful and neutral as compared to the happy stimuli; and a significant effect of group [$F(1, 43) = 12.73$, $p = 0.001$], indicating that the TD group outperformed those with WS. In addition, a condition by group interaction emerged [$F(1, 43) = 4.54$, $p < 0.04$]. Follow-up Bonferroni corrected t-test analyses (significance set at $p \leq 0.025$) showed that the interaction effect arose due to the fact that while both groups exhibited similar levels of performance with the social stimuli [$t(43) = -1.84$, $p = 0.07$], the performance of the WS group with the non-social stimuli was significantly lower than that of the TD group [$t(43) = -3.38$, $p < 0.01$]. More specifically, the TD group outperformed the WS group in the identification of fearful non-social stimuli [$t(43) = -2.63$, $p = 0.01$]. There were no other between group differences (all $p > 0.07$). Pair-wise t-tests comparing within-group performance across the social and non-social conditions showed that both groups of participants exhibited higher overall identification performance with the social as compared to the non-social stimuli [WS: $t(21) = 5.33$, $p < 0.001$; TD: $t(22) = 5.30$, $p < 0.001$].

An error analysis was then carried out. The dependent measure, i.e., the proportion of errors committed, was computed separately for the individual social and non-social affect categories. The frequency of incorrect social/non-social emotion identification responses was divided by the total number of errors committed for the targeted affect category inclusive of both social and non-social stimuli. For example, a participant who erroneously labeled four neutral faces as "happy" and two neutral faces as "scary" out of a total of 10 errors within the neutral affect category inclusive of social and non-social trials, yielded an error proportion of 0.40 for incorrect happy labels, and 0.20 incorrect scary labels, within the neutral social targets. Please note that the total number of trials inclusive of social and non-social conditions is 48. In order to explore any systematic patterns in participants' incorrect responses to the visual neutral stimuli, a condition (social/non-social) × error type (fearful/happy) × group (WS/TD) mixed ANOVA was conducted. Condition was included as an independent variable as well as error type, i.e., the incorrect emotion provided in place of the targeted affect. No significant results emerged for the neutral targets (all $p > 0.05$). For happy targets, significant main effects of condition

[$F(1, 43) = 541.92$, $p < 0.001$] and error type [$F(1, 43) = 591.28$, $p < 0.001$] emerged. More errors were made in identifying happy non-social ($M = 0.46$) as compared to happy social ($M = 0.004$) stimuli. Additionally, happy stimuli were more frequently incorrectly identified as neutral ($M = 0.46$) than fearful ($M = 0.001$). Finally, a condition × error type interaction reached significance [$F(1, 43) = 553.37$, $p < 0.001$], with happy non-social ($M = 0.92$) as compared to happy social ($M = 0.006$) stimuli being more frequently incorrectly identified as neutral [$t(44) = 23.72$, $p < 0.001$]. Bonferroni correction was employed for rest of the t-test analyses (significance set at $p \leq 0.025$). Participants mislabeled happy non-social images as neutral ($M = 0.92$) at a greater rate than misidentifying happy social stimuli as fearful [$M = 0.003$; $t(44) = 24.48$, $p < 0.001$]. For fearful affective targets, significant main effects of condition [$F(1, 43) = 8.94$, $p < 0.01$], error type [$F(1, 43) = 27.34$, $p < 0.001$], and group [$F(1, 43) = 8.62$, $p < 0.01$] were found. Incorrect identification of fearful stimuli occurred at a greater rate for non-social ($M = 0.24$) as compared to social ($M = 0.09$) images, and more errors were made in identifying fearful images as neutral ($M = 0.28$) than happy ($M = 0.05$). Participants with WS made more errors in identifying fearful stimuli as compared to the TD group ($M = 0.21$, $M = 0.12$, respectively). A significant interaction of condition × error type was observed [$F(1, 43) = 27.34$, $p < 0.001$], with fearful non-social stimuli being more frequently incorrectly identified as neutral ($M = 0.44$) than happy [$M = 0.04$; $t(44) = 5.12$, $p < 0.001$]. Finally, fearful non-social ($M = 0.46$) as compared to social ($M = 0.12$) stimuli were more frequently mislabeled as neutral [$t(44) = 3.46$, $p = 0.001$].

Psychophysiological results

Figure 2 describes the overall pattern of tonic EDA in WS and TD groups over trial number within the visual modality. The TD group showed a greater percentage change in tonic EDA as compared to the individuals with WS ($F = 14.11$, $p < 0.001$). A significant effect of trial number was found ($F = 14.69$, $p = 0.0001$), suggesting that habituation to the stimuli occurred over time during the experiment. However, there was a group by trial interaction, such that the habituation effect was predominantly observed in TD participants ($F = 8.81$, $p = 0.003$; see **Figure 2A**). Finally, there was no effect of emotion on tonic EDA ($p > 0.05$).

Analysis of the mean HR also revealed significant group differences, with a greater decrease in HR in the TD group as compared to those with WS ($F = 4.32$, $p = 0.04$). A main effect of trial number indicated an overall reduction in percentage change of HR decreased over time in both groups ($F = 9.51$, $p = 0.002$). Emotion modulated changes in HR ($F = 4.6$, $p = 0.01$), and pair-wise comparisons revealed that fearful stimuli elicited on average a greater decrease in HR in comparison to both happy and neutral emotional stimuli for both groups (both p's < 0.05). While there was no main effect of condition, a group by condition interaction emerged ($F = 4.48$, $p = 0.034$; see **Figure 2B**). Further exploration showed that this interaction was in part due to the differences between the WS and TD participants in the social condition only ($p < 0.05$), with a decrease in HR for the TD group, yet an overall increase in HR for individuals with WS when viewing faces.

Inter-beat interval measurement is based upon an analysis of individual heartbeat cycles, therefore changes in mean IBI between the baseline-level and that after stimulus onset is a sensitive method of quantifying heart beat acceleration/deceleration. The analysis of the mean IBI revealed significant main effects of group (WS change in mean IBI greater than that of TD group; $F = 5.7$, $p = 0.021$), emotion ($F = 7.07$, $p < 0.001$; larger change in mean IBI for fearful compared to other emotions, both p's < 0.05), and trial number (reduction of change in mean IBI over time; $F = 12.58$, $p < 0.001$). There was an interaction effect between emotion and condition ($F = 5.48$, $p < 0.001$), driven by a greater change in mean IBI for the fearful non-social condition in comparison to other non-social stimuli (both p's < 0.05). Further, there was a group by condition interaction ($F = 5.98$, $p = 0.015$), with individuals with WS displaying approximately zero mean change in IBI for the social condition, contrasting with a greater change in controls ($p < 0.05$; **Figure 2C**).

Figure 2 displays the sdIBI across conditions and groups (**Figure 2D**) and emotion across group (**Figure 2E**). The IBIs of participants with WS were more variable than those of the TD group ($F = 20.17$, $p < 0.0001$). A main effect of condition indicated that non-social conditions produced overall greater variability ($F = 4.69$, $p = 0.03$), while an interaction between group and condition highlighted that this increase in variability was attributable to the WS group ($F = 5.83$, $p < 0.02$). Further analyses of this interaction revealed increased sdIBI in the WS group as compared to participants with TD in the non-social condition, and increased sdIBI for the non-social relative to the social condition in WS only (all p's < 0.05; **Figure 2D**). A main effect of emotion was also found ($F = 6.76$, $p = 0.001$), suggesting that greater variability in IBI was observed for stimuli eliciting fearful as compared to happy and neutral emotions (all p's < 0.05). Finally, there was a trend for an interaction between group and emotion such that the IBIs of individuals with WS were greater in variance than those of the TD group's ($F = 2.88$, $p < 0.06$; **Figure 2E**), due to an ampler variation in response to happy ($p < 0.05$) and fearful emotional stimuli ($p = 0.07$).

BRIEF DISCUSSION

The goal of experiment 1 was to compare the processing of social and non-social visually presented affective stimuli at the levels of behavior and ANS responsivity in individuals with WS contrasted with a TD group. The main behavioral result showed that while individuals with WS performed at a comparable level to the TD comparison group in processing emotional faces, they were significantly poorer at identifying affect in non-social images. This result is in line with earlier studies (e.g., Järvinen-Pasley et al., 2010a,b) suggesting that WS is characterized by a bias toward social information manifesting as superior processing of social over non-social stimuli. An analysis of participants' error patterns further revealed that, in line with the existing literature, participants with WS showed difficulties in identifying fearful visual emotion as compared to the comparison group (e.g., Meyer-Lindenberg et al., 2005; Plesa Skwerer et al., 2009; Järvinen-Pasley et al., 2010c). Finally, in WS only, VIQ was positively correlated with affect identification in the social condition, suggesting parallel development of emotion recognition and linguistic capacities in our WS population. Indeed, it remains to be studied whether stronger linguistic abilities may enhance emotional understanding. This may be of

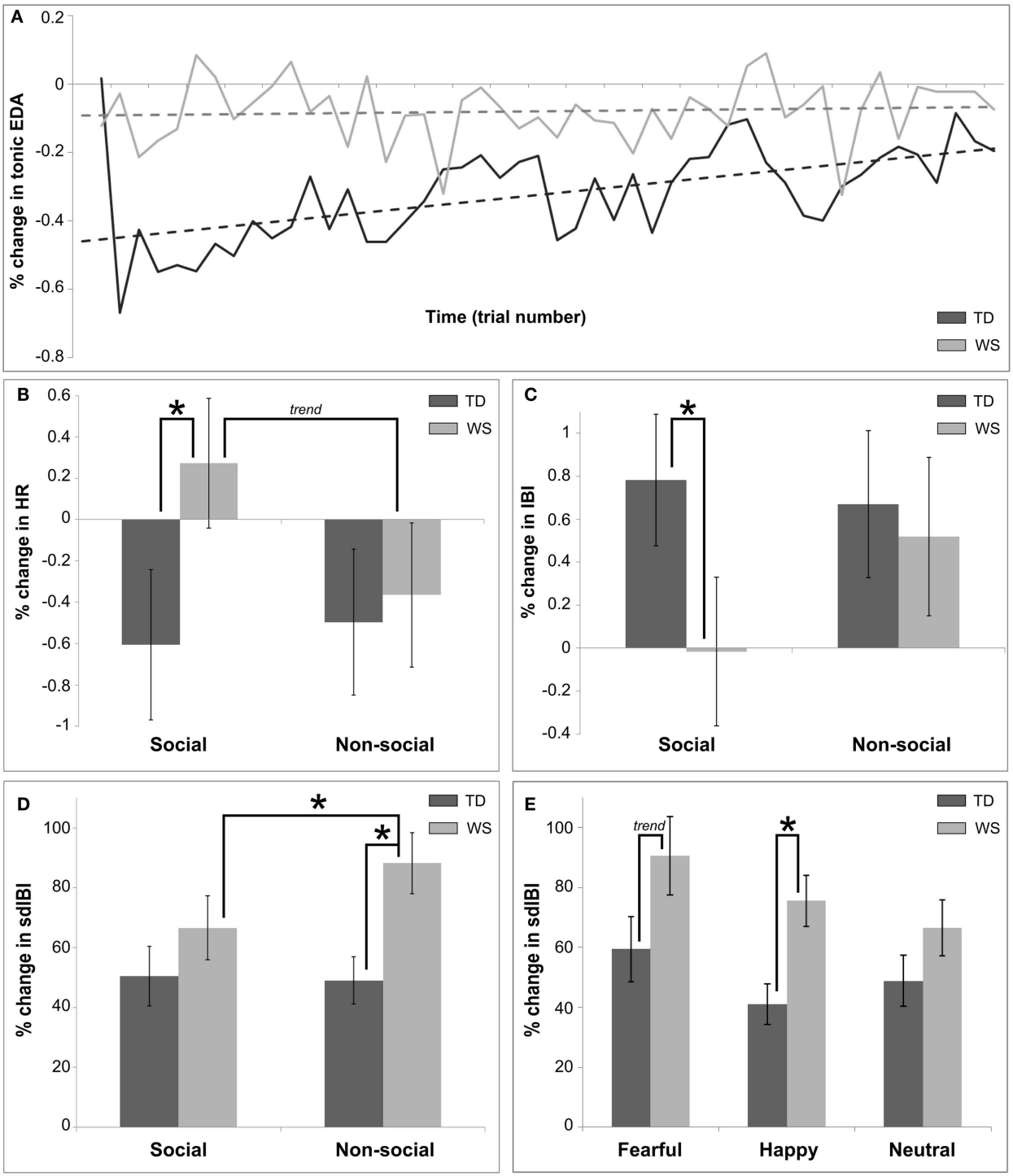

FIGURE 2 | Summary of main findings utilizing autonomic measures for Experiment 1, the visual modality. (A) Shows the differences in overall habituation over time between TD and WS participants, calculated as a percentage change between baseline (3 s pre-stimulus) and post stimulus (7 s after) in the mean tonic EDA. **(B)** Displays differences between social and non-social conditions in TD and WS participants, calculated as a percentage change between baseline and post stimulus in the mean HR. **(C)** Presents the differences between social and non-social conditions in TD and WS participants, calculated as a percentage change between baseline and post stimulus in the mean IBI. **(D)** Displays differences between social and non-social conditions in TD and WS participants, calculated as a percentage change between baseline and post stimulus in the sdIBI. **(E)** Displays differences between affective stimuli in TD and WS participants, calculated as a percentage change between baseline and post stimulus in the sdIBI.

specific importance to clinical populations with known emotional problems, e.g., autism.

An analysis of the ANS indices within the visual domain revealed many between group differences resulting from cardiovascular measures. First, it is noteworthy that individuals presenting with supravalvular aortic stenoses and hypertension, as is often the case in WS, do not show evident changes in raw ECG for quantification of the R peak and IBI, even if abnormalities in the QRS complex can be observed (see Dimopoulos et al., 2012, for an overview). Moreover, the use of change scores weighted at the baseline period rules out spurious differences in cardiovascular functioning. Notwithstanding these differences, the WS group showed an overall increase in mean HR for social stimuli in comparison to TD participants. This stands in contrast to previous publications demonstrating HR deceleration to dynamic face images in WS relative to controls (Plesa Skwerer et al., 2009). Furthermore, WS individuals showed decreased variation in heart periods (sdIBI) to faces in comparison to objects/scenes, similar to our behavioral results suggesting a greater emotional reactivity to faces in comparison to objects/scenes, since cardiac vagal reactivity is reduced for emotionally arousing stimuli. In the non-social condition, higher sdIBI can be thought of as indicating feelings of calm, equanimity, and control (Porges, 2007), yet in our WS population this possibly could be interpreted as attenuated emotional arousal in the non-social condition. Indeed, the significantly increased sdIBI and reduced performance in the non-social condition for WS individuals in contrast to controls, suggests diminished arousal in WS to non-face objects and scenes across all emotions. Similarly, an ampler response to happy and fearful stimuli for WS in comparison to TD individuals is not consistent with an interpretation of increased calmness, control, and so forth to happy or fearful face/object stimuli, but rather with the diminished arousal to non-face objects. Deterioration in performance observed in individuals with WS in relation to TD participants supports this view.

An analysis of the tonic EDA signal between the WS and TD groups revealed one striking difference. Whereas participants with TD showed a classical habituation effect over time, that is, reactivity to stimuli was attenuated as the trials progressed (see **Figure 2A**), individuals with WS showed patterns of responsivity that remained stable over time. Thus, our participants with WS did not habituate, regardless of their overall changes in EDA, in relation to TD individuals. This suggests significantly different rates of familiarization to affective visual stimuli across groups.

EXPERIMENT 2: VOCALIZATIONS vs. MELODIES: ANS SENSITIVITY TO AUDITORY SOCIAL AND NON-SOCIAL AFFECTIVE STIMULI

MATERIAL AND METHODS

Participants

Twenty individuals with WS (seven males) were recruited and screened as described under Experiment 1. All of these participants also participated in Experiment 1. Twenty-six TD comparison individuals (10 males) were also recruited and screened as described above. Twenty-two of these individuals also participated in Experiment 1, with psychophysiological analyses conducted on the same participants used for analysis in Experiment 1. Participants were administered a threshold audiometry test using a Welch Allyn AM232 manual audiometer, which was calibrated to ANSI s.3.21 (2004) standards. Auditory thresholds were assessed at 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 6000, and 8000 Hz, monaurally. The hearing of all participants included in the study was within the normal range.

Table 2 shows the demographic characteristics of the final sample of participants with WS and TD. The participants differed in terms of CA [$t(44) = 3.14$, $p = 0.003$] with the WS group being older than the TD group. The TD group scored significantly higher on VIQ, PIQ, and FSIQ (all $p < 0.001$). Pearson correlations exploring the potential contributions of CA, VIQ, PIQ, and FSIQ to task performance, showed no significant associations (WS: all $p > 0.43$, TD all $p > 0.09$).

Stimuli

For the social condition, the visual stimuli comprised 24 segments of non-linguistic vocal sounds (2–3 s/segment) taken from the "Montreal Affective Voices," a standardized set of vocal expressions without confounding linguistic information (freely)[2]. There were eight segments for each of three emotions (happy, fearful, and sad). The non-social condition included 24 segments of novel, normed musical pieces, eight segments eliciting each of three possible emotions (fearful, happy, sad). The segments of unfamiliar emotionally evocative music have been specifically composed by Marsha Bauman of Stanford University for studies to examine musical abilities in WS (see also Järvinen-Pasley et al., 2010a). These segments have been pre-tested in typical adults to confirm that they convey happy, fearful, or sad emotion with >95% accuracy.

Procedure

As in Experiment 1, the study had two phases: a passive version, which was always administered first (for psychophysiological measurement), and an active task, during which participants made affect identification judgments. EDA and ECG were recorded as described under Experiment 1, and the experimental apparatus were the same. A fixation cross was presented for 1000 ms before presentation of the stimulus, which were randomized with respect to both stimulus type (social/non-social) and affect valence (fearful/happy/sad). The duration of the auditory clips, presented at the onset of a 5000 ms blank screen, were slightly variable as described above, with human voices presented for an average of 1353 ± 642 ms, and music clips presented for 1354.67 ± 538.93 ms on average, since we required the stimuli to be as natural as possible. For example, an extended period of laughter might not elicit a happy emotional response. The inter-trial interval was 9000 ms, to again allow time for the autonomic levels to return to near baseline. Participants were told that they would hear short sounds that would either be a voice or music. For the passive task, participants were only instructed to listen to the sounds carefully while attending to a monitor displaying a fixation cross, and staying as quiet and still as possible. For the active task, participants were played the stimuli again sequentially, and asked to identify the emotion elicited by each sound. A response screen contained the words

[2]http://vnl.psy.gla.ac.uk/info.php?file=mav

"scared/scary," "happy," and "sad." The participants responded verbally, and the experimenter operated the computer keyboard on the participant's behalf.

RESULTS

Behavioral affect identification

Figure 3 displays the percentage of correct identifications within each affect category (fearful/happy/sad) across the social and non-social stimulus conditions in Experiment 2 for participants with WS and TD (total number of trials per affect category = 8).

The auditory affect identification data were analyzed by a $2 \times 3 \times 2$ repeated-measures ANOVA, with the condition (social/non-social) and emotion (fearful/happy/sad) entered as within-participants factors, and group (WS/TD) as a between-participants factor. This analysis revealed a significant main effect of condition [$F(1, 44) = 42.36$, $p < 0.001$], reflecting higher levels of performance overall with the social stimuli; a significant main effect of emotion [$F(2, 88) = 48.34$, $p < 0.001$], reflecting overall highest levels of identification of the happy as compared to the fearful and sad stimuli, and higher levels of identification of fearful, as compared to the sad stimuli; and a significant effect of group [$F(1, 44) = 13.84$, $p = 0.001$], indicating that the TD group outperformed those with WS. In addition, a condition by group interaction [$F(1, 44) = 9.85$, $p = 0.003$], a group by emotion interaction [$F(1, 88) = 6.33$, $p = 0.003$], and a condition by emotion by group interaction emerged [$F(1, 88) = 4.26$, $p < 0.02$]. Follow-up Bonferroni corrected t-test analyses (significance set at $p \leq 0.0125$) showed that the interaction effects emerged due to the fact that while both groups exhibited similar levels of performance with the social happy [$t(44) = -1.45$, $p = 0.15$] and social scary [$t(44) = -1.51$, $p = 0.14$] the TD group outperformed their counterparts with WS in identifying social sad [$t(44) = -2.06$, $p = 0.05$] stimuli. Within the non-social domain, again both groups yielded similar accuracy in recognizing non-social happy stimuli [$t(44) = -1.96$, $p = 0.06$)] while the TD group outperformed their counterparts with WS in identifying

Table 2 | Mean characteristics of the participant groups (SD; range in parentheses) in Experiment 2.

	CA (SD; range)	VIQ (SD; range)	PIQ (SD; range)	FSIQ (SD; range)
WS ($n = 20$)	27.2 (8.5; 13–46)	67 (8.4; 55–83)	63 (6.2; 53–72)	66 (7.2; 56–84)
TD ($n = 26$)	21.2 (4.3; 18–41)	113 (9.4; 89–128)	115 (7.4; 99–127)	115 (6.9; 99–126)

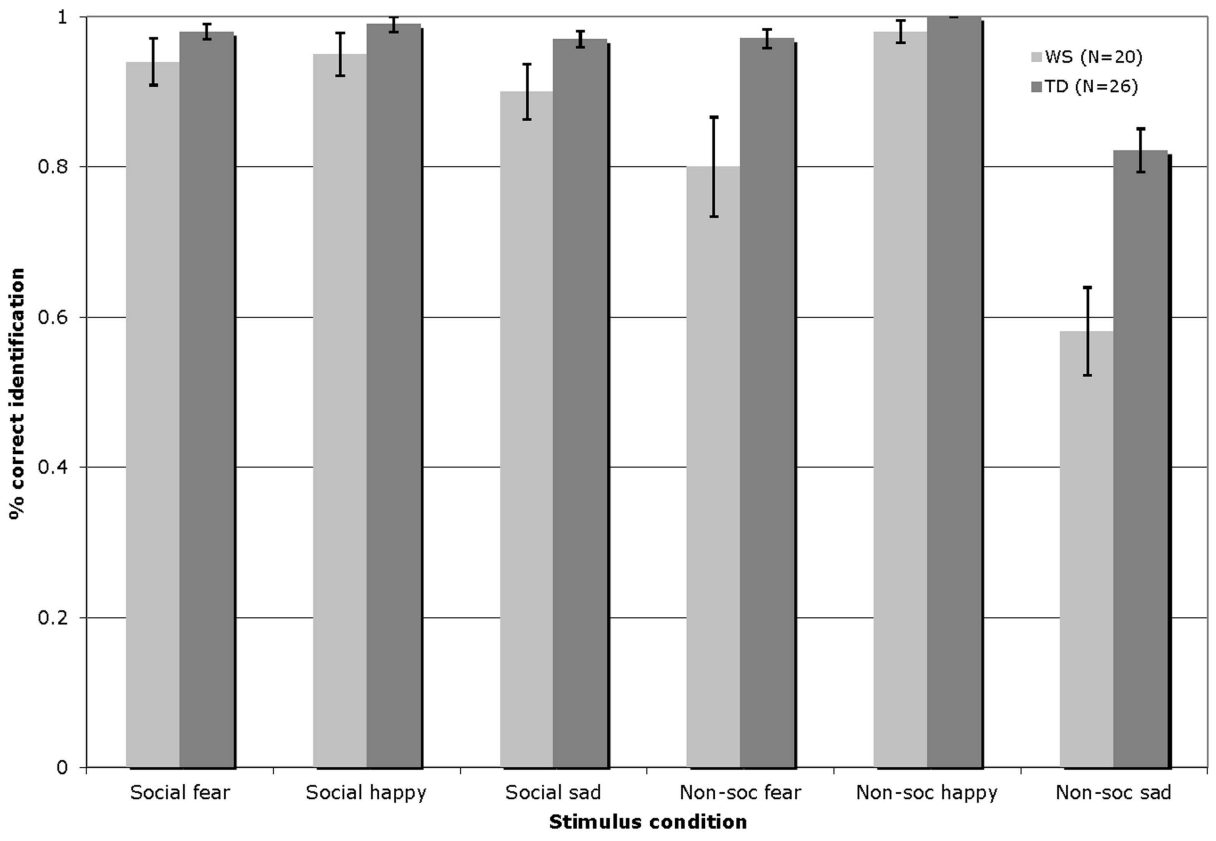

FIGURE 3 | Accuracy of auditory affect identification for individuals with WS and TD, across the happy, fearful, and sad categories for both social and non-social stimuli in Experiment 2 (Total number of trials per affect category = 8; Error bars represent ± 1 standard error mean, SEM).

both non-social fearful [$t(44) = -2.87, p = 0.006$], and non-social sad [$t(44) = -3.98, p < 0.001$] stimuli. Relative to those with WS, the TD group showed higher affect identification performance overall with both the social [$t(44) = -2.15,\ p = 0.04$] and the non-social [$t(44) = -4.03,\ p < 0.001$] stimuli. Pair-wise t-tests comparing within-group performance across the social and non-social conditions showed that whereas the WS participants exhibited similar identification performance across the happy social and non-social stimuli [$t(19) = -0.85,\ p = 0.41$] they showed higher identification performance with the fearful [$t(19) = 2.73,\ p = 0.013$)] and sad [$t(19) = 5.46,\ p < 0.001$)] social, as compared to the non-social fearful and sad stimuli. Overall, performance was significantly higher in the social, as compared to the non-social condition [$t(19) = 5.29, p < 0.001$]. Within-condition comparisons revealed that while the WS group showed similar performance across all emotions within the social condition {happy vs. fearful [$t(19) = 0.32,\ p = 0.76$], happy vs. sad [$t(19) = 1.80,\ p = 0.09$], fearful vs. sad [$t(19) = -0.96, p = 0.35$]}, with the non-social music stimuli, performance was higher with the happy, as compared to both the fearful [$t(19) = 2.75,\ p = 0.013$] and sad [$t(19) = 6.93,\ p < 0.001$] stimuli, and performance was higher with the fearful as compared to the sad non-social stimuli [$t(19) = 3.77,\ p = 0.001$]. By contrast, the TD participants performed similarly across the social and non-social conditions with the happy [$t(25) = -1.0, p = 0.33$] and fearful [$t(25) = 0.68,\ p = 0.50$] stimuli, while performance was significantly higher with the sad social as compared to sad non-social stimuli [$t(25) = 4.69,\ p < 0.001$]. Again, the performance of the TD group was significantly higher overall in the social, as compared with the non-social condition [$t(25) = 3.40,\ p = 0.002$]. Within-condition comparisons revealed that similarly to the WS group, the TD group showed comparable performance across all emotions within the social condition {happy vs. fearful [$t(25) = 0.52, p = 0.61$], happy vs. sad [$t(25) = 1.69,\ p = 1.0$)] fearful vs. sad [$t(25) = -0.81,\ p = 0.43$]}. With the non-social music stimuli, whereas performance was similar across the happy vs. the fearful music stimuli [$t(25) = 2.29, p = 0.03$], identification was higher with the happy vs. sad [$t(25) = 6.19, p < 0.001$], and scary vs. sad [$t(25) = 5.37,\ p < 0.001$] stimuli.

An error analysis was then carried out as described under Experiment 1. In order to explore any systematic patterns in participants' incorrect responses to the sad auditory stimuli, a condition (social/non-social) × error type (fearful/happy) × group (WS/TD) mixed ANOVA was conducted, analogous to the analysis within the visual domain. Main effects of condition [$F(1, 44) = 69.27,\ p < 0.001$] and error type [$F(1, 44) = 44.11,\ p < 0.001$] emerged, with more errors being made in identifying sad affect when the stimuli were non-social ($M = -0.38$) as compared to social ($M = 0.07$) in nature. In addition, a significant interaction between condition and error type was observed [$F(1, 44) = 28.39,\ p < 0.001$]. Bonferroni corrected t-tests (with significance set at $p \leq 0.025$) showed that participants made more errors in identifying sad stimuli as happy when it was non-social ($M = 0.64$) as compared to social [$M = 0.09$; $t(45) = 7.42,\ p < 0.001$] in nature. Finally, participants incorrectly identified sad non-social stimuli as happy ($M = 0.64$) more frequently than misidentifying sad non-social stimuli as fearful [$M = 0.10$; $t(45) = 6.72,\ p < 0.001$]. For happy targets, a significant main effect of group emerged [$F(1, 44) = 4.72,\ p < 0.05$], with participants with WS showing a higher overall error rate to the TD group ($M = 0.06$, $M = 0.01$, respectively). Finally, for fearful targets, the identification of non-social ($M = 0.04$) as compared to social ($M = 0.16$) stimuli resulted in greater rate of errors [$F(1, 44) = 8.47,\ p < 0.01$].

Psychophysiological results

As within the visual modality, the TD participants displayed a larger percentage change in tonic EDA as compared to those with WS ($F = 10.83,\ p = 0.002$). There were no other significant main effects (all p's > 0.05). There was a condition by trial number interaction ($F = 6.12,\ p < 0.02$), however, this is better explained by a three-way interaction with group ($F = 4.57,\ p = 0.03$; **Figures 4A,B**), highlighting that changes in tonic EDA were attenuated in participants with WS in comparison to the TD group for both social and non-social stimuli, but that the pattern of social and non-social stimuli in controls was highly variable over time. Moreover, a three-way interaction between emotion, condition and trial number ($F = 3.4, p = 0.03$) suggested that, for both groups, as trials progressed non-social stimuli elicited larger changes in tonic EDA than social stimuli, with this interaction predominantly driven by variable patterns of response to emotional stimuli over time.

An analysis of mean HR activity revealed a main effect of emotion ($F = 4.19,\ p < 0.02$), due in part to a trend for greater HR deceleration for stimuli eliciting sad emotions compared to happy emotions ($p < 0.09$). Moreover, the manipulation of social/non-social conditions produced a significantly greater decrease in HR for social voice stimuli in comparison to non-social music stimuli ($F = 4.15, p = 0.04$). A main effect of trial number ($F = 16.24,\ p = 0.0001$) suggested that the overall magnitude of the change in mean HR decreased over the duration of the experiment. No other comparison of mean HR reached significance (all p's > 0.05).

An analysis of the percentage change in mean IBI revealed main effects of condition (greater change for social compared to non-social stimuli, $F = 11.002, p < 0.001$), emotion ($F = 4.24,\ p = 0.015$; pair-wise comparison: sad stimuli produced a greater change in IBI than happy, $p = 0.09$), and trial number (reactivity to all stimuli decreasing over time, $F = 16.37, p = 0.0001$). There was a modulation between groups by condition ($F = 4.2,\ p < 0.04$), such that social stimuli elicited a greater mean change in IBI when compared to non-social stimuli in the WS group only (pair-wise trend, $p = 0.14$; see **Figure 4C**). Finally, a condition by trial number interaction emerged ($F = 5.31,\ p = 0.02$), suggesting that reactivity to social stimuli was higher across groups during early stages of the experiment compared to non-social stimuli.

Across time, both groups showed a decrease in the variation in IBI ($F = 4.38,\ p < 0.04$). In addition, the participants with WS displayed patterns of greater sdIBI variation as compared to the TD group ($F = 8.01,\ p < 0.01$). Finally, **Figure 4D** highlights the changes in sdIBI across emotions between groups, with the two factors significantly interacting ($F = 4.18,\ p = 0.015$). Individuals with WS as compared to the TD group showed a greater change in IBI variability for happy and sad stimuli (both p's < 0.05).

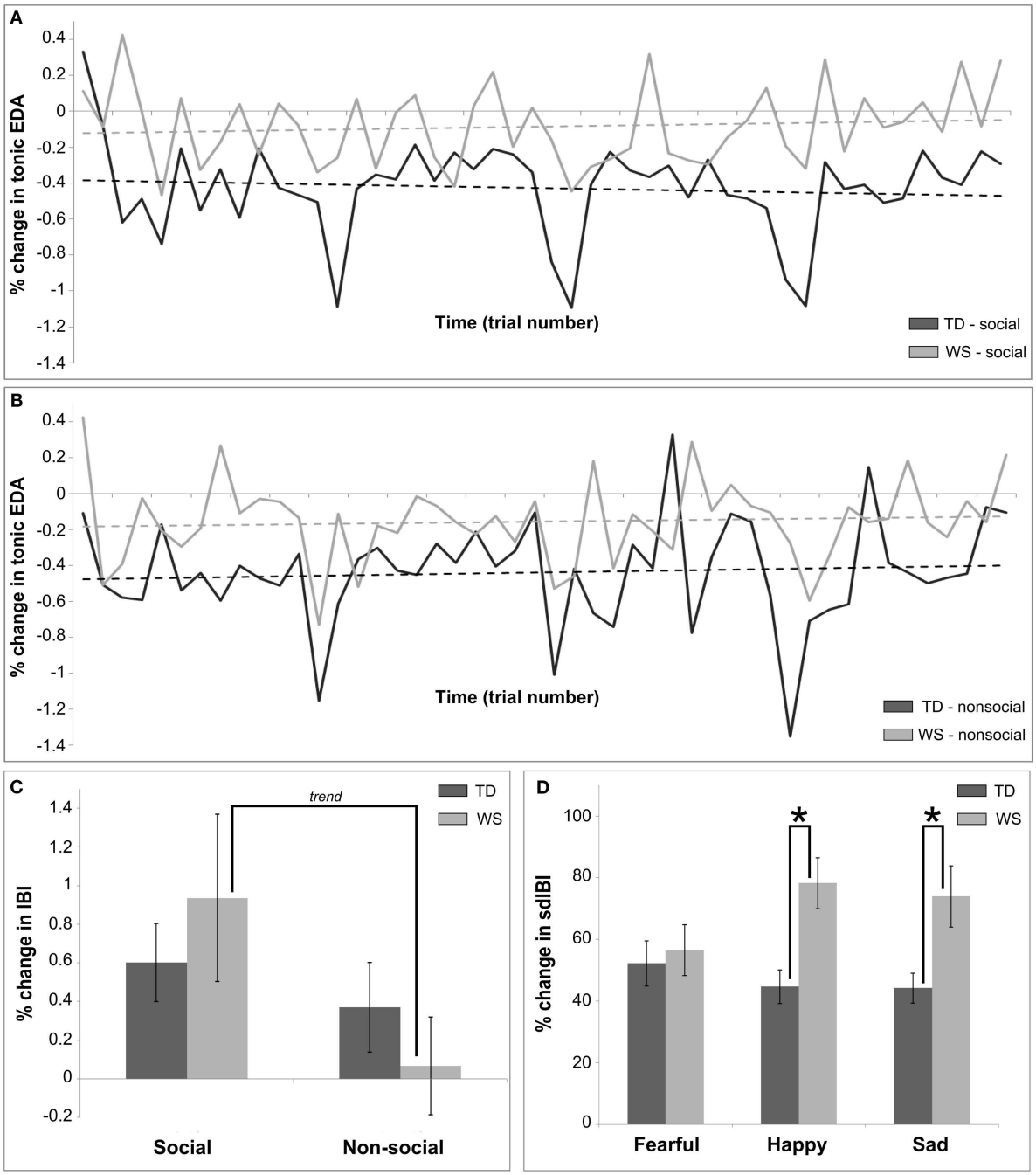

FIGURE 4 | Summary of main findings utilizing autonomic measures for Experiment 2, the auditory modality. (A) Shows the differences in habituation over time in the social condition between TD and WS participants, calculated as a percentage change between baseline and post stimulus in the mean tonic EDA. **(B)** Shows the differences in habituation over time in the non-social condition between TD and WS participants, calculated as a percentage change between baseline and post stimulus in the mean tonic EDA. **(C)** Presents the differences between social and non-social conditions in TD and WS participants, calculated as a percentage change between baseline and post stimulus in the mean IBI. **(D)** Displays differences between affective stimuli in TD and WS participants, calculated as a percentage change between baseline and post stimulus in the sdIBI.

BRIEF DISCUSSION

The main behavioral result from the auditory paradigm highlighted that the TD group outperformed those with WS in overall affect identification. However, within the social condition, individuals with WS showed comparable levels of accuracy to the TD group in identifying both happy and fearful vocalizations while showing specific deficits in the recognition of sad stimuli. This result is in partial agreement with our previous study,

reporting unimpaired identification of positive, and impaired processing of negative, human vocalizations, relative to CA-matched TD individuals (Järvinen-Pasley et al., 2010b). Moreover, Haas et al. (2009) found significantly attenuated neural (event-related potential measures) and amygdala activity (shown by functional magnetic resonance imaging, fMRI) to sad facial stimuli in individuals with WS relative to TD, which may underlie the poorer behavioral processing observed in the current experiment. However, in the former study, all negative vocalizations including, e.g., screams, grunts, and gasps were grouped under a single valence label (negative). Thus, the results may have been specifically due to individuals with WS making proportionally more errors with sad stimuli as compared to the stimuli conveying the other valences. Within the non-social condition, the performance of WS group was significantly poorer to that of TD individuals, mainly due to poor recognition of negatively valenced (fearful and sad) music. Consistent with this, Dykens et al. (2005) documented that individuals with WS reported feeling happy or upbeat feelings in response to negatively valenced music pieces in about 33% of trials in their study. Interestingly, when this tendency was related to the individuals' anxiety levels, it was found that positive feelings in response to negative music specifically characterized the persons with WS with the greatest fears and anxiety. Potential explanations offered by Dykens and coauthors included unawareness of negative affective states, or persistence toward positivity, in particularly anxious individuals with WS. However, in the present study, the performance of individuals with WS on the music trials was still above chance levels, indicating a globally preserved ability in affect recognition in our WS population to an essentially emotionally intangible stimulus class, i.e., music. An analysis of error patterns revealed only one between group difference, namely, individuals with WS made more errors as compared to the TD group in identifying both social and non-social happy stimuli.

Measures of autonomic activity revealed differences in WS and TD groups between reactivity to social (voice) and non-social (music) stimuli over time in the tonic EDA signal, such that individuals with WS exhibited reduced percentage change scores as compared to the TD participants. The three-way interaction observed is driven by the variable pattern of reactivity over time observed in the TD group (see **Figures 4A,B**). It is not plausible to claim, however, that it is similar to the lack of a habituation effect seen in the visual modality for WS, since across the conditions in the auditory modality, habituation of the tonic EDA was also not observed in the TD group.

Heart rate analysis revealed main effects of condition, emotion, and time. Across groups, decreases in HR were greater in relation to social as compared to non-social stimuli, and also for specific emotions (sad as compared to happy). Over time, HR deceleration was attenuated in both groups, caused by a converging baseline and post stimulus HR rate to a stable level throughout the experiment. This result suggests habituation in both groups to all stimuli. Further examination of sensitive IBI measures suggested differences in heart periods between social and non-social conditions in WS only, with a greater change in mean IBI seen for human vocalizations compared to music. This result stands in contrast to the visual modality, since, for visually presented images, heart period post stimulus deceleration was seen for non-social in comparison to social stimuli (**Figure 2C**), yet this finding failed to reach significance. Further, standard deviation of the IBI showed greater variability in response to happy and sad stimuli for individuals with WS in contrast to TD participants. The lack of increased variability to fear eliciting stimuli suggests increased vagal reactivity for happy and sad auditory clips in turn eliciting feelings of calm, equanimity, and control (Porges, 2007). This interpretation is not confounded by performance issues in WS since trial accuracy of participants was controlled for in our statistical model.

GENERAL DISCUSSION

The aim of the current multimodal study was to examine ANS sensitivity to both visually and aurally presented affect in individuals with WS, to elucidate one intriguing phenotypal WS characteristic: emotional reactivity and its relation to increased sociability. To our knowledge, no previous studies have addressed ANS indices in this syndrome in relation to auditory social (or non-social) information. In accordance with previous studies, individuals with WS exhibited higher levels of behavioral performance with the social as compared to non-social stimuli (e.g., Järvinen-Pasley et al., 2010a), within both visual and auditory modalities, while the TD comparison group showed similar levels of performance across the social and non-social conditions in both modalities, highlighting a "bias" toward social information in WS. The analysis of underlying ANS reactivity revealed striking differences between the groups. First, within the visual domain, ECG-derived analyses showed that while individuals with WS demonstrated HR acceleration for social stimuli, the TD group was characterized by deceleration, indexing significantly increased arousal to face stimuli in WS relative to TD. Second, individuals with WS demonstrated increased variation in heart periods (sdIBI) to non-face images in comparison to faces, suggesting a greater emotional reactivity to social in relation to non-social visual stimuli. Finally, the tonic EDA data indicated that, overall, whereas TD participants showed a classical habituation effect over time, that is, reactivity to stimuli was attenuated as the trials progressed, those with WS failed to habituate. In other words, individuals with WS showed significantly slower rate of familiarization to the affective visual stimuli as compared to their TD counterparts, to the point that there was no evidence of familiarization in the WS group. In the social domain, it is attractive to speculate that this aspect of ANS functioning may play a role in the increased attraction to faces and subsequent appetitive drive for affiliation in WS, as the lack of familiarization effect over time may also imply that such stimuli appear more novel for those with WS. However, further studies are needed to address this possibility. Furthermore, if WS individuals' perception of their environment retains its originality, it is plausible that social encounters are determined by the frequency and novelty of such opportunities to interact.

The current results from the visual domain highlight new directions in which psychophysiological functioning may underlie the WS social phenotype. In contrast to the previous findings of Plesa Skwerer et al. (2009), which indicated HR deceleration to dynamic face images in individuals with WS relative to controls, we found relatively increased HR for faces in WS. One possible reason for this difference between the studies may be due to the nature of the stimulus features used, i.e., static in the present study as compared

to dynamic in Plesa Skwerer et al.'s (2009) study. Moreover, the tonic EDA used in the current study provides a more global index of overall ANS functioning or tendency, rather than solely being a measure of ANS reactivity to particular stimuli, such as skin conductance spikes. Indeed, Riby et al. (2012) used tonic EDA as a measure of ANS sensitivity and found comparable reactivity to TD individuals when viewing live face stimuli in their sample of individuals with WS. On the other hand, phasic SCR spikes are most easily elicited by designs manipulating highly threatening or arousing situations (Lang et al., 1993; Lane et al., 1999), and as such this measure was not applicable to the current design. It is noteworthy that the individuals with WS tested by Plesa Skwerer et al. (2009) were younger in average (19 years) compared to the current sample (27 years). In the current study, age was further controlled for as a factor in the analyses, ruling out spurious differences in our sample affecting physiological measures. Similarly, time (trial number) was included as a factor in our models for both visual and auditory psychophysiological data. It is possible that this approach offers a new perspective on ANS functioning in WS, highlighting characteristics of the syndrome previously unseen, i.e., non-habituation to experimental stimuli. This result needs to be replicated with other measures, as well as other samples of participants with WS, to determine this effect as a feature of the WS social phenotype.

As mentioned above, the auditory paradigm produced differential results of ANS functioning relative to the visual experiment. This is not surprising in light of the fact that similar effects have been reported in the brain imaging literature, with visually presented affect resulting in more robust neural activation to aurally conveyed emotion (Adolphs, 2002, 2009). Specifically, while there is consensus of opinion that the amygdala represents a central subcortical structure involved in affective face processing, the literature is inconsistent regarding amygdala involvement in the processing of affective prosody (Scott et al., 1997; Anderson and Phelps, 1998; Adolphs and Tranel, 1999; Adolphs et al., 1999; Wildgruber et al., 2006). However, fMRI data illustrate the recruitment of the amygdala at least in the processing of fearful or threatening stimuli, regardless of their sensory modality (Dolan et al., 2001; Ethofer et al., 2006). The current results of ANS responsivity to auditory emotional stimuli in individuals with WS indicated decreased tonic EDA changes in response to both vocal and music stimuli in WS relative to the TD, suggestive of attenuated habituation to the stimuli; however, a similar pattern was also observed in the TD group.

Interestingly, the WS group was characterized by changes in heart periods for human vocalizations relative to music, suggesting reduced arousal to the social voice stimuli. The opposite pattern of reactivity was observed within the visual domain for individuals with WS, i.e., attenuated arousal to the non-social affective images relative to facial expressions of affect. These findings can be explained in terms of the polyvagal theory of cardiovascular functioning, which posits that the two branches of the vagus nerve support different behavioral systems. Specifically, the social engagement system is thought to be indexed by the activity of the myelinated vagus, through dampening of the HPA axis, in turn eliciting calm behavioral states (Porges, 2007). Our results suggest that, since heart beat deceleration has been linked with increased focused attention, essentially, human vocalizations were more engaging than our music stimuli. The absence of increased variability for fearful auditory stimuli in the WS group is in contrast to the aberrant reactions to fearful visual stimuli observed in such individuals in the current study, and with fMRI (Meyer-Lindenberg et al., 2005). Specifically, Meyer-Lindenberg et al. (2005) highlighted hypoactivation of the amygdala to fearful faces, and hyperactivation of the amygdala to fearful scenes, in individuals with WS relative to TD controls. However, valence-specific patterns of amygdala activation in response to face stimuli have also been reported in individuals with WS relative to TD controls (Haas et al., 2009). Consistent across modalities, individuals with WS as compared to the TD group showed significantly greater HR variability to happy stimuli, indexing increased vagal and thus parasympathetic involvement. Positive affective stimuli are more socially engaging, since they promote approach-related behaviors. Because the nuclei controlling muscles of the face and head are integrated with regulation of the myelinated vagus, there is a direct physiological link between HRV and social perception, interaction, and engagement. Furthermore, the control of the stapedius muscle in the middle ear, facilitating the recognition of human voices, is activated during raising of the eyelids, and thus also falls under control of the myelinated vagus (Porges, 2007). Hence, our experiment taps directly onto the preferred sensory channels for social engagement, interaction, and perception of information, suggesting atypical reactivity to positive affect in WS in both visual and auditory sensory systems.

The differences between ANS sensitivity in the visual and auditory modalities may reflect the relatively less clear affective cues provided by auditory, as compared to visual, stimuli, and associated differences in underlying neural processes (Adolphs, 2002, 2009). This pattern was also mirrored in behavioral performance, in that while accuracy remained stable across conditions and modalities for the TD participants, individuals with WS showed deterioration within the auditory domain, possibly due in part to the higher ambiguity of affect in auditory stimuli as compared to visual stimuli (cf. Adolphs, 2002, 2009). One possible explanation for the higher levels of performance of individuals with WS within the visual social domain, and the clearer pattern of ANS sensitivity to the visual social information, is that it may reflect the augmented salience of faces, and resultant attentional capture of such stimuli compared to non-social stimuli, in individuals with WS (Riby and Hancock, 2008, 2009). Using eye-tracking methodology, individuals with WS were found to fixate on people's faces and specifically on the eye region for significantly longer than individuals with TD and autism (Riby and Hancock, 2008). In another study using face stimuli embedded in scenes, individuals with WS displayed spared attentional capture to faces when finding embedded faces, exaggerated fixation, and a reduced tendency to disengage from the face stimuli, relative to both TD and autism comparison groups (Riby and Hancock, 2009). Alternatively, the current result showing attenuated arousal to the social as compared to non-social stimuli within the auditory domain, and the opposite pattern within the visual domain, in WS, may also reflect the special status that musical stimuli may have for such individuals. Indeed, behaviorally, individuals with WS have been described as showing unusually intense emotional responses

to music (Don et al., 1999; Levitin et al., 2004), while there are no such reports in relation to human vocalizations. It may thus be the case that including music as "non-social" stimulus does not provide an adequate or comparable contrast to human vocalizations, since music is potentially more interesting. Of relevance here are the fMRI findings of Levitin et al. (2003), who compared neural activation patterns to music and noise stimuli in individuals with WS. While TD individuals displayed greater activation in the superior temporal gyrus and the middle temporal gyri in response to music than to noise, the only region showing greater activation to music relative to noise stimuli in individuals with WS was the right amygdala. Thus, it may be that increased arousal to music stimuli in the current study relative to vocalizations reflects greater amygdala activation relative to other types of auditory stimuli in individuals with WS. Further investigations are warranted to clarify the neurobiological correlates of music vs. human affective voice processing in WS.

An alternative interpretation of HR reactivity that warrants discussion is linked to the characterization of the WS social phenotype, namely, that while individuals with WS display increased approach behaviors and overall increased social drive, they also exhibit a complex pattern of social anxieties (Dykens, 2003). In one model of social anxiety (Cook and Turpin, 1998), HR acceleration is considered as indicative of a defensive response to threatening stimuli, and has been directly linked to subjective feelings of fear and phobia (Elsesser et al., 2006), while HR deceleration is considered to reflect attentional orienting. Typically studies have reported increased HR acceleration in persons with high levels of social anxiety (e.g., Wieser et al., 2009). Thus, the profile of HR responsivity in individuals with WS in the current study appears to be consistent with those characterizing individuals with high social anxiety. However, the current stimuli cannot be considered as highly threatening due to their failure to elicit SCR spikes, which are characteristic of physiological reactivity to threatening/highly arousing social information. HR acceleration was observed, but this was not consistent for the fearful stimuli; rather, differences were selective across conditions and modalities. Consequently, it appears more plausible to interpret changes in HR as an index of arousal non-specific to fear.

In conclusion, the present study further extends the previous work on ANS functioning in WS, suggesting a more complex pattern indexed by EDA and cardiovascular reactivity. First, the lack of habituation observed in the EDA of individuals with WS suggests that visual information appears and remains affectively less familiar over time in WS, which might underlie two potentially intertwined aspects of the WS social phenotype – their increased desire to approach strangers and an unusually high attraction to faces (Mills et al., 2000; Riby and Hancock, 2008, 2009). Second, since our methods account for the known differences in normal heart functioning between WS and TD participants, we suggest that indices of cardiac activity can be just as informative when investigating physiological modulation to changes in affect. Further, differential patterns of responding at both behavioral and psychophysiological levels in WS (e.g., increased HR to faces) suggest acute autonomic reactivity to socially relevant stimuli (faces and voices) even if identification accuracy is lower relative to TD participants, which may underlie their increased emotional sensitivity and empathy as documented at the behavioral level (e.g., Tager-Flusberg and Sullivan, 2000). While it is tempting to highlight the increased appetitive drive for social interaction characterizing WS, our results suggest impairments in understanding emotion in non-social contexts. The overall pattern of increased ANS reactivity to social information in WS stands in sharp contrast to the profile reported for extraverted TD individuals as described in the introduction, and in fact resembles more of that associated with introversion. Future studies should further explore the unusual emotional sensitivity in WS in the context of specifically socially relevant information processing, to illuminate the basis of their unique social drive, together with the "peaks and valleys" characterizing the WS social phenotype across modalities.

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